(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 583 771 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
03.04.2013 Bulletin 2013/14

(21) Application number: **03800092.3**

(22) Date of filing: **22.12.2003**

(51) Int Cl.:
C12Q 1/68 *(2006.01)* ***C07K 14/47*** *(2006.01)*
C07K 14/705 *(2006.01)* ***C07K 16/18*** *(2006.01)*
C07K 16/28 *(2006.01)*

(86) International application number:
PCT/US2003/040978

(87) International publication number:
WO 2004/058052 (15.07.2004 Gazette 2004/29)

(54) **GENETIC POLYMORPHISMS ASSOCIATED WITH MYOCARDIAL INFARCTION, METHODS OF DETECTION AND USES THEREOF**

HERZINFARKT-ASSOZIIERTE GENETISCHE POLYMORPHIEN, NACHWEISVERFAHREN UND IHRE VERWENDUNG

POLYMORPHISMES GÉNÉTIQUES ASSOCIÉS A L'INFARCTUS DU MYOCARDE, PROCÉDÉS DE DÉTECTION ET LEURS UTILISATIONS

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR

(30) Priority: **20.12.2002 US 434778 P**
10.03.2003 US 453135 P
30.04.2003 US 466412 P
23.09.2003 US 504955 P

(43) Date of publication of application:
12.10.2005 Bulletin 2005/41

(60) Divisional application:
09172683.6 / 2 151 507
12163341.6 / 2 500 440
12163362.2 / 2 474 630
12163424.0 / 2 474 631
12163442.2 / 2 474 632

(73) Proprietor: **Celera Corporation**
Alameda, CA 94502 (US)

(72) Inventors:
- **CARGILL, Michele**
  Rockville, MD 20850 (US)
- **DEVLIN, James J.**
  Rockville, MD 20850 (US)
- **IAKOUBOVA, Olga**
  Rockville, MD 20850 (US)

(74) Representative: **Jones Day**
Rechtsanwälte, Attorneys-at-Law, Patentanwälte
Prinzregentenstrasse 11
80538 München (DE)

(56) References cited:
WO-A-01/18250 **WO-A-01/66800**
WO-A1-02/081689 **US-A1- 2002 155 446**

- **YAMADA Y ET AL: "Prediction of the risk of myocardial infarction from polymorphisms in candidate genes" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 347, no. 24, 12 December 2002 (2002-12-12), pages 1916-1923, XP002971561 ISSN: 0028-4793**
- **DATABASE DBSNP [Online] NCBI, US; 22 June 2001 (2001-06-22), "Reference SNP Cluster Report: rs2075252" XP002558673 retrieved from HTTP://WWW.NCBI.NLM.NIH.GOV/SNP/SNP_ REF.CG I?SEARCHTYPE=ADHOC_ SEARCH&TYPE=RS&RS=RS207 5252 Database accession no. rs2075252**
- **AUBO ET AL.: 'Risk of myocardial infarction associated with Gln/Arg 192 polymorphism in the human paraoxonase gene and diabetes mellitus' EUROPEAN HEART JOURNAL vol. 21, no. 1, January 2000, pages 33 - 38**

Printed by Jouve, 75001 PARIS (FR)

(Cont. next page)

- **TUOMAINEN ET AL.: 'Increased risk of acute myocardial infarction in carriers of the hemochromatosis gene Cys282Tyr mutation' CIRCULATION vol. 100, no. 12, September 1999, pages 1274 - 1279, XP009082573**
- **TAKAGI ET AL.: 'A GPVI polymorphism is a risk factor for myocardial infarction in Japanese' ATHEROSCLEROSIS vol. 165, no. 2, December 2002, pages 397 - 398, XP008099996**
- **DALEY ET AL.: 'The heart SNPs a beat: candidate polymorphisms in candidate genes for cardiovascular disease' TRENDS IN CARDIOVASCULAR MEDICINE vol. 11, no. 2, February 2001, pages 60 - 66, XP002335095**

Description

FIELD OF THE INVENTION

[0001] The present invention is in the field of myocardial infarction diagnosis. In particular, the present invention relates to specific single nucleotide polymorphisms (SNPs) in the human genome, and their association with myocardial infarction (including recurrent myocardial infarction) and related pathologies. Based on differences in allele frequencies in the myocardial infarction patient population relative to normal individuals, the naturally-occurring SNPs disclosed herein can be used as targets for the design of diagnostic reagents and the development of therapeutic agents, as well as for disease association and linkage analysis. In particular, the SNPs disclosed herein are useful for identifying an individual who is at an increased or decreased risk of developing myocardial infarction and for early detection of the disease, for providing clinically important information for the prevention and/or treatment of myocardial infarction, and for screening and selecting therapeutic agents. The SNPs disclosed herein are also useful for human identification applications. Methods, assays, kits, and reagents for detecting the presence of these polymorphisms and their encoded products are provided.

BACKGROUND OF THE INVENTION

Myocardial Infarction (including Recurrent Myocardial Infarction)

[0002] Myocardial infarction (MI) is the most common cause of mortality in developed countries. It is a multifactorial disease that involves atherogenesis, thrombus formation and propagation. Thrombosis can result in complete or partial occlusion of coronary arteries. The luminal narrowing or blockage of coronary arteries reduces oxygen and nutrient supply to the cardiac muscle (cardiac ischemia), leading to myocardial necrosis and/or stunning. MI, unstable angina, or sudden ischemic death are clinical manifestations of cardiac muscle damage. All three endpoints are part of the Acute Coronary Syndrome since the underlying mechanisms of acute complications of atherosclerosis are considered to be the same.

[0003] Atherogenesis, the first step of pathogenesis of MI, is a complex interaction between blood elements, mechanical forces, disturbed blood flow, and vessel wall abnormality. On the cellular level, these include endothelial dysfunction, monocytes/macrophages activation by modified lipoproteins, monocytes/macrophages migration into the neointima and subsequent migration and proliferation of vascular smooth muscle cells (VSMC) from the media that results in plaque accumulation.

[0004] In recent years, an unstable (vulnerable) plaque was recognized as an underlying cause of arterial thrombotic events and MI. A vulnerable plaque is a plaque, often not stenotic, that has a high likelihood of becoming disrupted or eroded, thus forming a thrombogenic focus. Two vulnerable plaque morphologies have been described. A first type of vulnerable plaque morphology is a rupture of the protective fibrous cap. It can occur in plaques that have distinct morphological features such as large and soft lipid pool with distinct necrotic core and thinning of the fibrous cap in the region of the plaque shoulders. Fibrous caps have considerable metabolic activity. The imbalance between matrix synthesis and matrix degradation thought to be regulated by inflammatory mediators combined with VSMC apoptosis are the key underlying mechanisms of plaque rupture. A second type of vulnerable plaque morphology, known as "plaque erosion", can also lead to a fatal coronary thrombotic event. Plaque erosion is morphologically different from plaque rupture. Eroded plaques do not have fractures in the plaque fibrous cap, only superficial erosion of the intima. The loss of endothelial cells can expose the thrombogenic subendothelial matrix that precipitates thrombus formation. This process could be regulated by inflammatory mediators. The propagation of the acute thrombi for both plaque rupture and plaque erosion events depends on the balance between coagulation and thrombolysis. MI due to a vulnerable plaque is a complex phenomenon that includes: plaque vulnerability, blood vulnerability (hypercoagulation, hypothrombolysis), and heart vulnerability (sensitivity of the heart to ischemia or propensity for arrhythmia).

[0005] Recurrent myocardial infarction can generally be viewed as a severe form of MI progression caused by multiple vulnerable plaques that are able to undergo pre-rupture or a pre-erosive state, coupled with extreme blood coagulability.

[0006] The incidence of MI is still high despite currently available preventive measures and therapeutic intervention. More than 1,500,000 people in the US suffer acute MI each year (many without seeking help due to unrecognized MI), and one third of these people die. The lifetime risk of coronary artery disease events at age 40 years is 42.4% for men (one in two) and 24.9% for women (one in four) (Lloyd-Jones DM; Lancet, 1999 353: 89-92).

[0007] The current diagnosis of MI is based on the levels or troponm I or T that indicate the cardiac muscle progressive necrosis, impaired electrocardiogram (ECG), and detection of abnormal ventricular wall motion or angiographic data (the presence of acute thrombi). However, due to the asymptomatic nature of 25% of acute MIs (absence of atypical chest pain, low ECG sensitivity), a significant portion of MIs are not diagnosed and therefore not treated appropriately (e.g., prevention of recurrent MIs).

[0008] Despite a very high prevalence and lifetime risk of MI, there are no good prognostic markers that can identify an individual with a high risk of vulnerable plaques and justify preventive treatments. MI risk assessment and prognosis is currently done using classic risk factors or the recently introduced Framingham Risk Index. Both of these assessments put a significant weight on LDL levels to justify preventive treatment. However, it is well established that half of all MIs occur in individuals without overt hyperlipidemia. Hence, there is a need for additional risk factors for predicting predisposition to MI.

[0009] Other emerging risk factors are inflammatory biomarkers such as C-reactive protein (CRP), ICAM-1, SAA, TNF a, homocysteine, impaired fasting glucose, new lipid markers (ox LDL, Lp-a, MAD-LDL, etc.) and pro-thrombotic factors (fibrinogen, PAI-1). Despite showing some promise, these markers have significant limitations such as low specificity and low positive predictive value, and the need for multiple reference intervals to be used for different groups of people (e.g., males-females, smokers-non smokers, hormone replacement therapy users, different age groups). These limitations diminish the utility of such markers as independent prognostic markers for MI screening.

[0010] Genetics plays an important role in MI risk. Families with a positive family history of MI account for 14% of the general population, 72% of premature MIs, and 48% of all MIs (Williams R R, Am J Cardiology, 2001; 87:129). In addition, replicated linkage studies have revealed evidence of multiple regions of the genome that are associated with MI and relevant to MI genetic traits, including regions on chromosomes 14, 2, 3 and 7 (Broeckel U, Nature Genetics, 2002; 30: 210; Harrap S, Arterioscler Thromb Vasc Biol, 2002; 22: 874-878, Shearman A, Human Molecular Genetics, 2000, 9; 9,1315-1320), implying that genetic risk factors influence the onset, manifestation, and progression of MI. Recent association studies have identified allelic variants that are associated with acute complications of coronary heart disease, including allelic variants of the ApoE, ApoA5, Lpa, APOCIII, and Klotho genes.

[0011] Genetic markers such as single nucleotide polymorphisms are preferable to other types of biomarkers. Genetic markers that are prognostic for MI can be genotyped early in life and could predict individual response to various risk factors. The combination of serum protein levels and genetic predisposition revealed by genetic analysis of susceptibility genes can provide an integrated assessment of the interaction between genotypes and environmental factors, resulting in synergistically increased prognostic value of diagnostic tests.

[0012] Thus, there is an urgent need for novel genetic markers that are predictive of predisposition to MI, particularly for individuals who are unrecognized as having a predisposition to MI. Such genetic markers may enable prognosis of MI in much larger populations compared with the populations which can currently be evaluated by using existing risk factors and biomarkers. The availability of a genetic test may allow, for example, appropriate preventive treatments for acute coronary events to be provided for susceptible individuals (such preventive treatments may include, for example, statin treatments and statin dose escalation, as well as changes to modifiable risk factors), lowering of the thresholds for ECG and angiography testing, and allow adequate monitoring of informative biomarkers.

[0013] Moreover, the discovery of genetic markers associated with MI will provide novel targets for therapeutic intervention or preventive treatments of MI, and enable the development of new therapeutic agents for treating MI and other cardiovascular disorders.

SNPs

[0014] The genomes of all organisms undergo spontaneous mutation in the course of their continuing evolution, generating variant forms of progenitor genetic sequences (Gusella, Ann. Rev. Biochem. 55, 831-854 (1986)). A variant form may confer an evolutionary advantage or disadvantage relative to a progenitor form or may be neutral. In some instances, a variant form confers an evolutionary advantage to the species and is eventually incorporated into the DNA of many or most members of the species and effectively becomes the progenitor form. Additionally, the effects of a variant form may be both beneficial and detrimental, depending on the circumstances. For example, a heterozygous sickle cell mutation confers resistance to malaria, but a homozygous sickle cell mutation is usually lethal. In many cases, both progenitor and variant forms survive and co-exist in a species population. The coexistence of multiple forms of a genetic sequence gives rise to genetic polymorphisms, including SNPs.

[0015] Approximately 90% of all polymorphisms in the human genome are SNPs. SNPs are single base positions in DNA at which different alleles, or alternative nucleotides, exist in a population. The SNP position (interchangeably referred to herein as SNP, SNP site, or SNP locus) is usually preceded by and followed by highly conserved sequences of the allele (e.g., sequences that vary in less than 1/100 or 1/1000 members of the populations). An individual may be homozygous or heterozygous for an allele at each SNP position. A SNP can, in some instances, be referred to as a "cSNP" to denote that the nucleotide sequence containing the SNP is an amino acid coding sequence.

[0016] A SNP may arise from a substitution of one nucleotide for another at the polymorphic site. Substitutions can be transitions or transversions. A transition is the replacement of one purine nucleotide by another purine nucleotide, or one pyrimidine by another pyrimidine. A transversion is the replacement of a purine by a pyrimidine, or vice versa. A SNP may also be a single base insertion or deletion variant referred to as an "indel" (Weber et al., "Human diallelic insertion/deletion polymorphisms", Am J Hum Genet 2002 Oct;71(4):854-62).

[0017] A synonymous codon change, or silent mutation/SNP (terms such as "SNP", "polymorphism", "mutation", "mutant", "variation", and "variant" are used herein interchangeably), is one that does not result in a change of amino acid due to the degeneracy of the genetic code. A substitution that changes a codon coding for one amino acid to a codon coding for a different amino acid (i.e., a non-synonymous codon change) is referred to as a missense mutation. A nonsense mutation results in a type of non-synonymous codon change in which a stop codon is formed, thereby leading to premature termination of a polypeptide chain and a truncated protein. A read-through mutation is another type of non-synonymous codon change that causes the destruction of a stop codon, thereby resulting in an extended polypeptide product. while SNPs can be bi-, tri-, or tetra- allelic, the vast majority of the SNPs are bi-allelic, and are thus often referred to as "bi-allelic markers", or "di-allelic markers".

[0018] As used herein, references to SNPs and SNP genotypes include individual SNPs and/or haplotypes, which are groups of SNPs that are generally inherited together. Haplotypes can have stronger correlations with diseases or other phenotypic effects compared with individual SNPs, and therefore may provide increased diagnostic accuracy in some cases (Stephens et al. Science 293, 489-493, 20 July 2001).

[0019] Causative SNPs are those SNPs that produce alterations in gene expression or in the expression, structure, and/or function of a gene product, and therefore are most predictive of a possible clinical phenotype. One such class includes SNPs falling within regions of genes encoding a polypeptide product, i.e. cSNPs. These SNPs may result in an alteration of the amino acid sequence of the polypeptide product (i.e., non-synonymous codon changes) and give rise to the expression of a defective or other variant protein. Furthermore, in the case of nonsense mutations, a SNP may lead to premature termination of a polypeptide product. Such variant products can result in a pathological condition, e.g., genetic disease. Examples of genes in which a SNP within a coding sequence causes a genetic disease include sickle cell anemia and cystic fibrosis.

[0020] Causative SNPs do not necessarily have to occur in coding regions; causative SNPs can occur in, for example, any genetic region that can ultimately affect the expression, structure, and/or activity of the protein encoded by a nucleic acid. Such genetic regions include, for example, those involved in transcription, such as SNPs in transcription factor binding domains, SNPs in promoter regions, in areas involved in transcript processing, such as SNPs at intron-exon boundaries that may cause defective splicing, or SNPs in mRNA processing signal sequences such as polyadenylation signal regions. Some SNPs that are not causative SNPs nevertheless are in close association with, and therefore segregate with, a disease-causing sequence. In this situation, the presence of a SNP correlates with the presence of, or predisposition to, or an increased risk in developing the disease. These SNPs, although not causative, are nonetheless also useful for diagnostics, disease predisposition screening, and other uses.

[0021] An association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder of interest, such as myocardial infarction, and comparing the information to that of controls (i.e., individuals who do not have the disorder; controls may be also referred to as "healthy" or "normal" individuals) who are preferably of similar age and race. The appropriate selection of patients and controls is important to the success of SNP association studies. Therefore, a pool of individuals with well-characterized phenotypes is extremely desirable.

[0022] A SNP may be screened in diseased tissue samples or any biological sample obtained from a diseased individual, and compared to control samples, and selected for its increased (or decreased) occurrence in a specific pathological condition, such as pathologies related to myocardial infarction. Once a statistically significant association is established between one or more SNP(s) and a pathological condition (or other phenotype) of interest, then the region around the SNP can optionally be thoroughly screened to identify the causative genetic locus/sequence(s) (e.g., causative SNP/mutation, gene, regulatory region, etc.) that influences the pathological condition or phenotype. Association studies may be conducted within the general population and are not limited to studies performed on related individuals in affected families (linkage studies).

[0023] Clinical trials have shown that patient response to treatment with pharmaceuticals is often heterogeneous. There is a continuing need to improve pharmaceutical agent design and therapy. In that regard, SNPs can be used to identify patients most suited to therapy with particular pharmaceutical agents (this is often termed "pharmacogenomics"). Similarly, SNPs can be used to exclude patients from certain treatment due to the patient's increased likelihood of developing toxic side effects or their likelihood of not responding to the treatment. Pharmacogenomics can also be used in pharmaceutical research to assist the drug development and selection process. (Linder et al. (1997), Clinical Chemistry, 43, 254; Marshall (1997), Nature Biotechnology, 15, 1249; International Patent Application WO 97/40462, Spectra Biomedical; and Schafer et al. (1998), Nature Biotechnology, 16, 3).

[0024] WO 01/66800 A identifies polymorphisms which can predispose individuals to disease.

[0025] DATABASE DBSNP NCBI, US (22 June 2001) accession no. rs2075252 discloses a polymorphic site in the human genome.

[0026] Yamada et al. ("Prediction of the risk of myocardial infarction from polymorphisms in candidate genes" NEW ENGLAND JOURNAL OF MEDICINE, vol. 347, no. 24,12 December 2002, pages 1916-1923) describes that the risk of myocardial infarction was significantly associated with teh C1019T polymporphism in the connexin 37 gene in men and

the 4G-668/5G polymorphism in the plasminogen-activator inhibitor type 1 gene and the 5A-1171/6A polymorphism in the stromelysin-1 gene in women.

SUMMARY OF THE INVENTION

[0027] The present invention relates to the identification of a SNP that is associated with recurrent myocardial infarction and related pathologies. The polymorphisms disclosed herein are directly useful as targets for the design of diagnostic reagents and the development of therapeutic agents for use in the diagnosis and treatment of myocardial infarction and related pathologies.

[0028] Based on the identification of a SNP associated with recurrent myocardial infarction, the present invention also provides methods of detecting this variant as well as the design and preparation of detection reagents needed to accomplish this task. The invention specifically provides a use of a SNP in genetic sequences involved in myocardial infarction in a method for determining whether a human has an increased risk for recurrent myocardial infarction. Described herein are variant proteins encoded by nucleic acid molecules containing such SNPs, antibodies to the encoded variant proteins, computer-based and data storage systems containing the novel SNP information. The invention provides methods of detecting the SNP in a test sample, methods of identifying individuals who have an altered (i.e., increased or decreased) risk for recurrent myocardial infarction based on the presence of the SNP disclosed herein or its encoded product. For reference only, the description provides methods of identifying individuals who are more or less likely to respond to a treatment, methods of screening for compounds useful in the treatment of a disorder associated with a variant gene/protein, compounds identified by these methods, and methods of treating disorders mediated by a variant gene/protein. The present invention provides methods of using the SNP disclosed herein for human identification.

[0029] In Tables 1-2, the present invention provides gene information, transcript sequences (SEQ ID NOS:1), encoded amino acid sequences (SEQ ID NOS:2), genomic sequences (SEQ ID NOS:4), transcript-based context sequences (SEQ ID NOS:3) and genomic-based context sequences (SEQ ID NOS:5) that contain the SNP described herein, and extensive SNP information that includes observed alleles, allele frequencies, populations/ethnic groups in which alleles have been observed, information about the type of SNP and corresponding functional effect, and, for cSNPs, information about the encoded polypeptide product. The transcript sequence (SEQ ID NO: 1), amino acid sequence (SEQ ID NO: 2), genomic sequence (SEQ ID NO:4), transcript-based SNP context sequence (SEQ ID NO:3), and genomic-based SNP context sequence (SEQ ID NO:5) are also provided in the Sequence Listing.

[0030] In a specific embodiment of the present invention, a naturally-occurring SNP in the human genome is provided. This SNPs is associated with recurrent myocardial infarction such that it can have a variety of uses in the diagnosis and/or treatment of recurrent myocardial infarction. An alternative embodiment, of the invention is the use of an amplified polynucleotide, which is produced by amplification of a SNP-containing nucleic acid template in the method of the present invention. In another aspect, described is a variant protein which is encoded by a nucleic acid molecule containing a SNP disclosed herein.

[0031] In yet another embodiment of the invention, the use of a reagent for detecting a SNP in the context of its naturally-occurring flanking nucleotide sequences (which can be, e.g., either DNA or mRNA) in the method of the present invention is provided. In particular, such a reagent may be in the form of, for example, a hybridization probe or an amplification primer that is useful in the specific detection of a SNP. For reference only, a protein detection reagent is used to detect a variant protein which is encoded by a nucleic acid molecule containing a SNP disclosed herein. For example, a protein detection reagent is an antibody or an antigen-reactive antibody fragment.

[0032] Also provided in the invention is the use of kits comprising SNP detection reagents, in the method of the present invention and methods for detecting the SNP disclosed herein by employing detection reagents. In a specific embodiment, the present invention provides for a method of identifying an individual having an increased or decreased risk of developing myocardial infarction by detecting the presence or absence of a SNP allele disclosed herein. In an aspect, a method for diagnosis of an increased risk for recurrent myocardial infarction by detecting the presence or absence of a SNP allele disclosed herein is described.

[0033] The nucleic acid molecules described herein can be inserted in an expression vector, such as to produce a variant protein in a host cell. Thus, described herein is also a vector comprising a SNP-containing nucleic acid molecule, genetically-engineered host cells containing the vector, and methods for expressing a recombinant variant protein using such host cells. The described host cells, SNP-containing nucleic acid molecules, and/or variant proteins can be used as targets in a method for screening and identifying therapeutic agents or pharmaceutical compounds useful in the treatment of myocardial infarction.

[0034] An aspect described herein is a method for treating myocardial infarction in a human subject wherein said human subject harbors a gene, transcript, and/or encoded protein identified in Tables 1-2, which method comprises administering to said human subject a therapeutically or prophylactically effective amount of one or more agents counteracting the effects of the disease, such as by inhibiting (or stimulating) the activity of the gene, transcript, and/or encoded protein identified in Tables 1-2.

[0035] Another aspect described herein is a method for identifying an agent useful in therapeutically or prophylactically treating myocardial infarction in a human subject wherein said human subject harbors a gene, transcript, and/or encoded protein identified in Tables 1-2, which method comprises contacting the gene, transcript, or encoded protein with a candidate agent under conditions suitable to allow formation of a binding complex between the gene, transcript, or encoded protein and the candidate agent and detecting the formation of the binding complex, wherein the presence of the complex identifies said agent.

[0036] Another aspect described herein is a method for treating myocardial infarction in a human subject, which method comprises:

(i) determining that said human subject harbors a gene, transcript, and/or encoded protein identified in Tables 1-2, and
(ii) administering to said subject a therapeutically or prophylactically effective amount of one or more agents counteracting the effects of the disease.

[0037] Many other uses and advantages of the present invention will be apparent to those skilled in the art upon review of the detailed description of the preferred embodiments herein. Solely for clarity of discussion, the invention is described in the sections below by way of non-limiting examples.

DESCRIPTION OF THE SEQUENCE LISTING

[0038] The Sequence Listing provides the transcript sequence (SEQ ID NO:1) and protein sequence (SEQ ID NO:2), and genomic sequence (SEQ ID NO:4) for the myocardial infarction-associated gene that contains the SNP of the present invention. Also provided in the Sequence Listing are context sequences flanking each SNP, including both transcript-based context sequence (SEQ ID NO:3) and genomic-based context sequence (SEQ ID NO.5). The context sequences generally provide 100bp upstream (5') and 100bp downstream (3') of each SNP, with the SNP in the middle of the context sequence, for a total of 200bp of context sequence surrounding each SNP.

DESCRIPTION OF TABLE 1 AND TABLE 2

[0039] Table 1 and Table 2 disclose the SNP and associated gene/transcript/protein information used in the method of the present invention. For gene number 29, Table 1 and Table 2 each provide a header containing gene/transcript/protein information, followed by a transcript and protein sequence (in Table 1) or genomic sequence (in Table 2), and then SNP information regarding the SNP used in the present invention found in that gene/transcript.

[0040] NOTE: The SNP is include in both Table 1 and Table 2; Table 1 presents the SNP relative to its transcript sequence and encoded protein sequence, whereas Table 2 presents the SNPs relative to its genomic sequence. The SNP can readily be cross-referenced between Tables based on its hCV identification number.

[0041] The gene/transcript/protein information includes:

- a gene number (1 through n, where n = the total number of genes in the Table)
- a Celera hCG and UID internal identification numbers for the gene
- a Celera hCT and UID internal identification numbers for the transcript (Table 1 only)
- a public Genbank accession number (e.g., RefSeq NM number) for the transcript (Table 1 only)
- a Celera hCP and UID internal identification numbers for the protein encoded by the hCT transcript (Table 1 only)
- a public Genbank accession number (e.g., RefSeq NP number) for the protein (Table 1 only)
- an art-known gene symbol
- an art-known gene/protein name
- Celera genomic axis position (indicating start nucleotide position-stop nucleotide position)
- the chromosome number of the chromosome on which the gene is located
- an OMIM (Online Mendelian Inheritance in Man; Johns Hopkins University/NCBI) public reference number for obtaining further information regarding the medical significance of each gene
- alternative gene/protein name(s) and/or symbol(s) in the OMIM entry NOTE: Due to the presence of alternative splice forms, multiple transcript/protein entries can be provided for a single gene entry in Table 1; i.e., for a single Gene Number, multiple entries may be provided in series that differ in their transcript/protein information and sequences.

[0042] Following the gene/transcript/protein information is a transcript sequence and protein sequence (in Table 1), or a genomic sequence (in Table 2), for each gene, as follows:

- transcript sequence (Table 1 only) (corresponding to SEQ ID NO:1 of the Sequence Listing), with SNPs identified

by their IUB codes (transcript sequences can include 5' UTR, protein coding, and 3' UTR regions). (NOTE: If there are differences between the nucleotide sequence of the hCT transcript and the corresponding public transcript sequence identified by the Genbank accession number, the hCT transcript sequence (and encoded protein) is provided, unless the public sequence is a RefSeq transcript sequence identified by an NM number, in which case the RefSeq NM transcript sequence (and encoded protein) is provided. However, whether the hCT transcript or RefSeq NM transcript is used as the transcript sequence, the disclosed SNPs are represented by their IUB codes within the transcript.)

- the encoded protein sequence (Table 1 only) (corresponding to SEQ ID NO:2 of the Sequence Listing)
- the genomic sequence of the gene (Table 2 only), including 6kb on each side of the gene boundaries (i.e., 6kb on the 5' side of the gene plus 6kb on the 3' side of the gene) (corresponding to SEQ ID NO:4 of the Sequence Listing).

[0043] NOTE: The transcript, protein, and transcript-based SNP context sequences are provided in both Table 1 and in the Sequence Listing. The genomic and genomic-based SNP context sequences are provided in both Table 2 and in the Sequence Listing. SEQ ID NOS are indicated in Table 1 for each transcript sequence (SEQ ID NO:1), protein sequence (SEQ ID NO:2), and transcript-based SNP context sequence (SEQ ID NO:3), and SEQ ID NOS are indicated in Table 2 for each genomic sequence (SEQ ID NO:4), and genomic-based SNP context sequence (SEQ ID NO:5).

[0044] The SNP information includes:

- context sequence (taken from the transcript sequence in Table 1, and taken from the genomic sequence in Table 2) with the SNP represented by its IUB code, including 100 bp upstream (5') of the SNP position plus 100 bp downstream (3') of the SNP position (the transcript-based SNP context sequences in Table 1 are provided in the Sequence Listing as SEQ ID NO:3; the genomic-based SNP context sequences in Table 2 are provided in the Sequence Listing as SEQ ID NO:5).
- Celera hCV internal identification number for the SNP (in some instances, an "hDV" number is given instead of an "hCV" number)
- SNP position [position of the SNP within the given transcript sequence (Table 1) or within the given genomic sequence (Table 2)]
- SNP source (may include any combination of one or more of the following five codes, depending on which internal sequencing projects and/or public databases the SNP has been observed in: "Applera" = SNP observed during the re-sequencing of genes and regulatory regions of 39 individuals, "Celera" = SNP observed during shotgun sequencing and assembly of the Celera human genome sequence, "Celera Diagnostics" = SNP observed during re-sequencing of nucleic acid samples from individuals who have myocardial infarction or a related.pathology, "dbSNP" = SNP observed in the dbSNP public database, "HGBASE" = SNP observed in the HGBASE public database, "HGMD" = SNP observed in the Human Gene Mutation Database (HGMD) public database) (NOTE: multiple "Applera"' source entries for a single SNP indicate that the same SNP was covered by multiple overlapping amplification products and the re-sequencing results (e.g., observed allele counts) from each of these amplification products is being provided)
- Population/allele/allele count information in the format of [population1(allele1,count|allele2,count) population2(allele1,count| allele2,count) total (allele1,total count|allele2,total count)]. The information in this field includes populations/ethnic groups in which particular SNP alleles have been observed ("cau" = Caucasian, "his" = Hispanic, "chn" = Chinese, and "afr" = African-American, "jpn" = Japanese, "ind" = Indian, "mex" = Mexican, "ain" = "American Indian, "cra" = Celera donor, "no_pop" = no population information available), identified SNP alleles, and observed allele counts (within each population group and total allele counts), where available ["-" in the allele field represents a deletion allele of an insertion/deletion ("indel") polymorphism (in which case the corresponding insertion allele, which may be comprised of one or more nucleotides, is indicated in the allele field on the opposite side of the "|"); "-"in the count field indicates that allele count information is not available].

[0045] NOTE: For SNPs of "Applera" SNP source, genes/regulatory regions of 39 individuals (20 Caucasians and 19 African Americans) were re-sequenced and, since each SNP position is represented by two chromosomes in each individual (with the exception of SNPs on X and Y chromosomes in males, for which each SNP position is represented by a single chromosome), up to 78 chromosomes were genotyped for each SNP position. Thus, the sum of the African-American ("afr") allele counts is up to 38, the sum of the Caucasian allele counts ("cau") is up to 40, and the total sum of all allele counts is up to 78.

[0046] (NOTE: semicolons separate population/allele/count information corresponding to each indicated SNP source; i.e., if four SNP sources are indicated, such as "Celera", "dbSNP", "HGBASE", and "HGMD", then population/allele/count information is provided in four groups which are separated by semicolons and listed in the same order as the listing of SNP sources, with each population/allele/count information group corresponding to the respective SNP source

based on order; thus, in this example, the first population/allele/count information group would correspond to the first listed SNP source (Celera) and the third population/allele/count information group separated by semicolons would correspond to the third listed SNP source (HGBASE); if population/allele/count information is not available for any particular SNP source, then a pair of semicolons is still inserted as a place-holder in order to maintain correspondence between the list of SNP sources and the corresponding listing of population/allele/count information)

- SNP type (e.g., location within gene/transcript and/or predicted functional effect) ["MIS-SENSE MUTATION" = SNP causes a change in the encoded amino acid (i.e., a non-synonymous coding SNP); "SILENT MUTATION" = SNP does not cause a change in the encoded amino acid (i.e., a synonymous coding SNP); "STOP CODON MUTATION" = SNP is located in a stop codon; "NONSENSE MUTATION" = SNP creates or destroys a stop codon; "UTR 5" = SNP is located in a 5' UTR of a transcript; "UTR 3" = SNP is located in a 3' UTR of a transcript; "PUTATIVE UTR 5" = SNP is located in a putative 5' UTR; "PUTATIVE UTR 3" = SNP is located in a putative 3' UTR; "DONOR SPLICE SITE" = SNP is located in a donor splice site (5' intron boundary); "ACCEPTOR SPLICE SITE" = SNP is located in an acceptor splice site (3' intron boundary); "CODING REGION" = SNP is located in a protein-coding region of the transcript; "EXON" = SNP is located in an exon; "INTRON" = SNP is located in an intron; "hmCS" = SNP is located in a human-mouse conserved segment; "TFBS" = SNP is located in a transcription factor binding site; "UNKNOWN" = SNP type is not defined; "INTERGENIC" = SNP is intergenic, i.e., outside of any gene boundary]
- Protein coding information (Table 1 only), where relevant, in the format of [protein SEQ ID NO:#, amino acid position, (amino acid-1, codon1) (amino acid-2, codon2)]. The information in this field includes SEQ ID NO of the encoded protein sequence, position of the amino acid residue within the protein identified by the SEQ ID NO that is encoded by the codon containing the SNP, amino acids (represented by one-letter amino acid codes) that are encoded by the alternative SNP alleles (in the case of stop codons, "X" is used for the one-letter amino acid code), and alternative codons containing the alternative SNP nucleotides which encode the amino acid residues (thus, for example, for missense mutation-type SNPs, at least two different amino acids and at least two different codons are generally indicated; for silent mutation-type SNPs, one amino acid and at least two different codons are generally indicated, etc.). In instances where the SNP is located outside of a protein-coding region (e.g., in a UTR region), "None" is indicated following the protein SEQ ID NO.

DESCRIPTION OF TABLE 5

[0047] Table 5 provides sequences (SEQ ID NOS:6,7,8) of primers that have been synthesized and used in the laboratory to carry out allele-specific PCR reactions in order to assay the SNPs disclosed in Table 7 during the course of myocardial infarction association studies.

[0048] Table 5 provides the following:

- the column labeled "hCV" provides an hCV identification number for each SNP site
- the column labeled "Alleles" designates the two alternative alleles at the SNP site identified by the hCV identification number that are targeted by the allele-specific primers (the allele-specific primers are shown as "Sequence A" and "Sequence B" in each row)
- the column labeled "Sequence A (allele-specific primer)" provides an allele-specific primer that is specific for the first allele designated in the "Alleles" column
- the column labeled "Sequence B (allele-specific primer)" provides an allele-specific primer that is specific for the second allele designated in the "Alleles" column
- the column labeled "Sequence C (common primer)" provides a common primer that is used in conjunction with each of the allele-specific primers (the "Sequence A" primer and the "Sequence B" primer) and which hybridizes at a site away from the SNP position.

[0049] All primer sequences are given in the 5' to 3' direction.

[0050] Each of the alleles designated in the "Alleles" column matches the 3' nucleotide of the allele-specific primer that is specific for that allele. Thus, the first allele designated in the "Alleles" column matches the 3' nucleotide of the "Sequence A" primer, and the second allele designated in the "Alleles" column matches the 3' nucleotide of the "Sequence B" primer.

DESCRIPTION OF TABLE 7

[0051] Table 7 provide results of statistical analyses for SNPs disclosed in Tables 1, 2, and 5 (SNPs can be cross-referenced between Tables based on their hCV identification numbers). Table 7 provides statistical results for association of SNPs with recurrent myocardial infarction (RMI). The statistical results shown in Table 7 provides support for the

association of the SNP with RMI. For example, the statistical results provided in Table 7 show that the association of the SNP with RMI is supported by p-values < 0.05 in at least one of three genotypic association tests and/or an allelic association test. Moreover, in general, the SNP identified in Table 7 is a SNP for which the association with RMI has been replicated by virtue of being significant in at least two independently collected sample sets, which further verifies the association of this SNP with RMI. Furthermore, results of stratification-based analyses are also provided; stratified analysis can, for example, enable increased prediction of RMI risk via interaction between conventional risk factors (stratum) and SNP.

[0052] NOTE: SNP can be cross-referenced between Table 1, 2, 5 and 7 based on its hCV identification number

[0053] TABLE 7 (SNP association with Recurrent Myocardial Infarction)

Description of column headings for Table 7:

Table 7 column heading	Definition
Gene	Locus Link HUGO approved gene symbol
Marker	Internal hCV identification number for the tested SNP
Sample Set	Sample Set used in the analysis (CARE, Pre-CARE or WGS_S0012)
p-value	Result of the asymptotic chi square test for allelic association, dominant genotypic association, recessive genotypic association, or the allelic, dominant, or recessive p-value of the stratified analysis
OR	odds ratio
95%CI	95% confidence interval of the given odds ratio
Case_Freq	Allele frequency of minor allele in cases
Control_Freq	Allele frequency of minor allele in controls
Allele1	Nucleotide (allele) of the tested SNP for which statistics are being reported
Mode	The mode of inheritance
Strata	Indicates if the analysis of the dataset was based on a substratum such as gender, age, BMI, Hypertension, Fasting Glucose levels, etc. (strata are described below)

[0054] Definition of entries in the "Strata" column (Table 7) for stratification-based analyses:

Stratum	Definition
BMI_TERTILE_1	Individuals in the lowest tertile of body mass index
BMI_TERTILE_2	Individuals in the middle tertile of body mass index
BMI_TERTILE_3	Individuals in the highest tertile of body mass index
PLACEBO	Patients who were in placebo arm of the CARE trail
PRAVASTATIN	Patients who were in Pravastatin arm of the CARE trail
MALE	Only males
FEMALE	Only females
HYPERTEN_1	Individuals with history of Hypertension
HYPERTEN _0	Individuals without history of Hypertension
GLUCOSE_TERTILE_1	Individuals in a lowest tertile of Fasting Glucose levels
GLUCOSE_TERTILE_2	Individuals in a middle tertile of Fasting Glucose levels
GLUCOSE_TERTILE_3	Individuals in a highest tertile of Fasting Glucose levels
AGE_TERTILE_1	Individuals in a lowest tertile of age (premature MI)
AGE_TERTILE_2	Individuals in a middle tertile of age
AGE_TERTILE_3	Individuals in a highest tertile age

(continued)

Stratum	Definition
EVERSMOKED_0	Individuals wh0 never smoked
EVERSMOKED_1	Former smokers
EVERSMOKED_2	Current smokers
FMHX_CHD_1	Individuals with family history of CHD
FMHX_CHD_0	Individuals without family history of CHD

DESCRIPTION OF THE FIGURE

[0055] Figure 1 provides a diagrammatic representation of a computer-based discovery system containing the SNP information described herein in computer readable form.

DETAILED DESCRIPTION OF THE INVENTION

[0056] The present invention provides a method for determining whether a human has an increased risk for recurrent myocardial infarction (MI), comprising:

a) testing nucleic acid from said human for the presence or absence of a polymorphism in gene *LRP2* at position 101 of SEQ ID NO:5 or its complement; and
b) correlating the presence of G at position 101 of SEQ ID NO:5 or C at position 101 of its complement with said human having said increased risk for recurrent M1, or the absence of said G or said C with said human having no said increased risk for recurrent MI.

[0057] In another aspect of the invention, provided is a use of an isolated nucleic acid 5 molecule comprising at least 8 contiguous nucleotides of SEQ ID NO: 5, wherein said at least 8 contiguous nucleotides of SEQ ID NO: 5 include position 101 of SEQ ID NO: 5, or the complement thereof, in any one of the methods of the present invention.
[0058] The invention further provides a use of an amplified polynucleotide containing the single nucleotide polymorphism (SNP) at position 101 of SEQ ID NO:5, or the complement thereof, in the method according to any one of the methods of the present invention, wherein the amplified polynucleotide is between about 16 and about 1,000 nucleotides in length.
[0059] The invention also provides a use of an isolated polynucleotide which specifically hybridizes to a nucleic acid molecule containing the single nucleotide polymorphism (SNP) at position 101 of SEQ ID NO: 5, or the complement thereof, in any one of the methods of the present invention.
[0060] In another aspect of the invention, provided is a use of a test kit comprising a container containing a SNP detection reagent which detects the presence of G or A at position 101 of SEQ ID NO:5 or C or T at position 101 of its complement in any one of the methods of the present invention.
[0061] The present invention provides the use of a SNP associated with recurrent myocardial infarction and, nucleic acid molecules containing the SNP in the method of the present invention, and methods for the detection of the SNP. Described herein are uses of SNPs for the development of detection reagents. The invention provides the use of kits that utilize such reagents in the methods of the present invention. The myocardial infarction-associated SNPs disclosed herein are useful for diagnosing, screening for, and evaluating predisposition to myocardial infarction and related pathologies in humans. Furthermore, such SNPs and their encoded products are useful targets for the development of therapeutic agents.
[0062] A large number of SNPs have been identified from re-sequencing DNA from 39 individuals, and they are indicated as "Applera" SNP source in Tables 1-2. Their allele frequencies observed in each of the Caucasian and African-American ethnic groups are provided. Additional SNPs described herein were previously identified during shotgun sequencing and assembly of the human genome. Furthermore, the information provided in Table 1-2, particularly the allele frequency information obtained from 39 individuals and the identification of the precise position of the SNP within each gene/transcript, allows haplotypes (i.e., groups of SNPs that are co-inherited) to be readily inferred.
[0063] Described herein are novel SNPs associated with myocardial infarction, as well as SNPs that were previously known in the art, but were not previously known to be associated with myocardial infarction. Accordingly, disclosed herein are novel compositions and methods based on the novel SNPs disclosed herein, and also novel methods of using the known, but previously unassociated, SNPs in methods relating to myocardial infarction (e.g., for diagnosing myocardial

infarction, etc.). In Tables 1-2, the known SNP is identified based on the public database in which it has been observed, which is indicated as one or more of the following SNP types: "dbSNP" = SNP observed in dbSNP, "HGBASE" = SNP observed in HGBASE, and "HGMD" = SNP observed in the Human Gene Mutation Database (HGMD).

[0064] Particular SNP alleles described herein can be associated with either an increased risk of having or developing myocardial infarction, or a decreased risk of having or developing myocardial infarction. SNP alleles that are associated with a decreased risk of having or developing myocardial infarction may be referred to as "protective" alleles, and SNP alleles that are associated with an increased risk of having or developing myocardial infarction may be referred to as "susceptibility" alleles or "risk factors". Thus, whereas certain SNPs (or their encoded products) can be assayed to determine whether an individual possesses a SNP allele that is indicative of an increased risk of having or developing myocardial infarction (i.e., a susceptibility allele), other SNPs (or their encoded products) can be assayed to determine whether an individual possesses a SNP allele that is indicative of a decreased risk of having or developing myocardial infarction (i.e., a protective allele). Similarly, particular SNP alleles described herein can be associated with either an increased or decreased likelihood of responding to a particular treatment or therapeutic compound, or an increased or decreased likelihood of experiencing toxic effects from a particular treatment or therapeutic compound. The term "altered" may be used herein to encompass either of these two possibilities (e.g., an increased or a decreased risk/likelihood).

[0065] Those skilled in the art will readily recognize that nucleic acid molecules may be double-stranded molecules and that reference to a particular site on one strand refers, as well, to the corresponding site on a complementary strand. In defining a SNP position, SNP allele, or nucleotide sequence, reference to an adenine, a thymine (uridine), a cytosine, or a guanine at a particular site on one strand of a nucleic acid molecule also defines the thymine (uridine), adenine, guanine, or cytosine (respectively) at the corresponding site on a complementary strand of the nucleic acid molecule. Thus, reference may be made to either strand in order to refer to a particular SNP position, SNP allele, or nucleotide sequence. Probes and primers, may be designed to hybridize to either strand and SNP genotyping methods disclosed herein may generally target either strand. Throughout the specification, in identifying a SNP position, reference is generally made to the protein-encoding strand, only for the purpose of convenience.

[0066] References to variant peptides, polypeptides, or proteins described herein include peptides, polypeptides, proteins, or fragments thereof, that contain at least one amino acid residue that differs from the corresponding amino acid sequence of the art-known peptide/polypeptide/protein (the art-known protein may be interchangeably referred to as the "wild-type", "reference", or "normal" protein). Such variant peptides/polypeptides/proteins can result from a codon change caused by a nonsynonymous nucleotide substitution at a protein-coding SNP position (i.e., a missense mutation) described herein. Variant peptides/polypeptides/proteins described herein can also result from a nonsense mutation, i.e. a SNP that creates a premature stop codon, a SNP that generates a read-through mutation by abolishing a stop codon, or due to any SNP described herein that otherwise alters the structure, function/activity, or expression of a protein, such as a SNP in a regulatory region (e.g. a promoter or enhancer) or a SNP that leads to alternative or defective splicing, such as a SNP in an intron or a SNP at an exon/intron boundary. As used herein, the terms "polypeptide", "peptide", and "protein" are used interchangeably.

ISOLATED NUCLEIC ACID MOLECULES AND SNP DETECTION REAGENTS & KITS

[0067] Tables 1 and 2 provide a variety of information about the SNP used in the method of the present invention that is associated with recurrent myocardial infarction, including the transcript sequence (SEQ ID NO:1), genomic sequence (SEQ ID NO:2), and protein sequence (SEQ ID NO:2) of the encoded gene products (with the SNPs indicated by IUB codes in the nucleic acid sequences). In addition, Tables 1 and 2 include SNP context sequences, which generally include 100 nucleotide upstream (5') plus 100 nucleotides downstream (3') of each SNP position (SEQ ID NO:3 correspond to transcript-based SNP context sequence disclosed in Table 1, and SEQ ID NO:5 correspond to genomic-based context sequences disclosed in Table 2), the alternative nucleotides (alleles) at each SNP position, and additional information about the variant where relevant, such as SNP type (coding, missense, splice site, UTR, etc.), human populations in which the SNP was observed, observed allele frequencies, information about the encoded protein, etc.

Isolated Nucleic Acid Molecules

[0068] The present invention provides the use of isolated nucleic acid molecules that contain the SNP disclosed in Table 1 and/or Table 2 in the method of the present invention. Isolated nucleic acid molecules containing the SNP disclosed in Tables 1 and 2 may be interchangeably referred to throughout the present text as "SNP-containing nucleic acid molecules". Isolated nucleic acid molecules may optionally encode a full-length variant protein or fragment thereof. The isolated nucleic acid molecules described herein also include probes and primers (which are described in greater detail below in the section entitled "SNP Detection Reagents"), which may be used for assaying the disclosed SNPs, and isolated full-length genes, transcripts, cDNA molecules, and fragments thereof, which may be used for such purposes as expressing an encoded protein.

[0069] As used herein, an "isolated nucleic acid molecule" generally is one that contains a SNP described herein or one that hybridizes to such molecule such as a nucleic acid with a complementary sequence, and is separated from most other nucleic acids present in the natural source of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule containing a SNP as used in the method of the present invention, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. A nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered "isolated". Nucleic acid molecules present in non-human transgenic animals, which do not naturally occur in the animal, are also considered "isolated". For example, recombinant DNA molecules contained in a vector are considered "isolated". Further examples of "isolated" DNA molecules include recombinant DNA molecules maintained in heterologous host cells, and purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include in vivo or in vitro RNA transcripts of the isolated SNP-containing DNA molecules, described herein. Isolated nucleic acid molecules described herein further include such molecules produced synthetically.

[0070] Generally, an isolated SNP-containing nucleic acid molecule comprises one or more SNP positions disclosed herein with flanking nucleotide sequences on either side of the SNP positions. A flanking sequence can include nucleotide residues that are naturally associated with the SNP site and/or heterologous nucleotide sequences. Preferably the flanking sequence is up to about 500, 300, 100, 60, 50, 30, 25, 20, 15, 10, 8, or 4 nucleotides (or any other length in-between) on either side of a SNP position, or as long as the full-length gene or entire protein-coding sequence (or any portion thereof such as an exon), especially if the SNP-containing nucleic acid molecule is to be used to produce a protein or protein fragment.

[0071] For full-length genes and entire protein-coding sequences, a SNP flanking sequence can be, for example, up to about 5KB, 4KB, 3KB, 2KB, 1KB on either side of the SNP. Furthermore, in such instances, the isolated nucleic acid molecule comprises exonic sequences (including protein-coding and/or non-coding exonic sequences), but may also include intronic sequences. Thus, any protein coding sequence may be either contiguous or separated by introns. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences and is of appropriate length such that it can be subjected to the specific manipulations or uses described herein such as recombinant protein expression, preparation of probes and primers for assaying the SNP position, and other uses specific to the SNP-containing nucleic acid sequences.

[0072] An isolated SNP-containing nucleic acid molecule can comprise, for example, a full-length gene or transcript, such as a gene isolated from genomic DNA (e.g., by cloning or PCR amplification), a cDNA molecule, or an mRNA transcript molecule. Polymorphic transcript sequence is provided in Table 1 and in the Sequence Listing (SEQ ID NO:1), and polymorphic genomic sequence is provided in Table 2 and in the Sequence Listing (SEQ ID NO:4). Furthermore, the use of fragments of such full-length genes and transcripts that contain the SNP disclosed herein in the method of the present invention is also encompassed by the present invention, and such fragments may be used, for example, to express any part of a protein, such as a particular functional domain or an antigenic epitope.

[0073] Thus, the present invention also encompasses the use of fragments of the nucleic acid sequences provided in Tables 1-2 (transcript sequence is provided in Table 1 as SEQ ID NO:1, genomic sequence is provided in Table 2 as SEQ ID NO:4, transcript-based SNP context sequence is provided in Table 1 as SEQ ID NO:3, and genomic-based SNP context sequence is provided in Table 2 as SEQ ID NO:5) and their complement in the method of the present invention. A fragment typically comprises a contiguous nucleotide sequence at least about 8 or more nucleotides, more preferably at least about 12 or more nucleotides, and even more preferably at least about 16 or more nucleotides. Further, a fragment could comprise at least about 18, 20, 22, 25, 30, 40, S0, 60,100, 250 or 500 (or any other number in-between) nucleotides in length. The length of the fragment will be based on its intended use. For example, the fragment can encode epitope-bearing regions of a variant peptide or regions of a variant peptide that differ from the normal/wild-type protein, or can be useful as a polynucleotide probe or primer. Such fragments can be isolated using the nucleotide sequences provided in Table 1 and/or Table 2 for the synthesis of a polynucleotide probe. A labeled probe can then be used, for example, to screen a cDNA library, genomic DNA library, or mRNA to isolate nucleic acid corresponding to the coding region. Further, primers can be used in amplification reactions, such as for purposes of assaying one or more SNPs sites or for cloning specific regions of a gene.

[0074] An isolated nucleic acid molecule as used in the method of the present invention further encompasses a SNP-containing polynucleotide that is the product of any one of a variety of nucleic acid amplification methods, which are used to increase the copy numbers of a polynucleotide of interest in a nucleic acid sample. Such amplification methods are well known in the art, and they include but are not limited to, polymerase chain reaction (PCR) (U.S. Patent Nos. 4,683,195; and 4,683,202; PCR Technology: Principles and Applications for DNA Amplification, ed. H.A. Erlich, Freeman Press, NY, NY, 1992), ligase chain reaction (LCR) (Wu and Wallace, Genomics 4:560, 1989; Landegren et al., Science 241:1077, 1988), strand displacement amplification (SDA) (U.S. Patent Nos. 5,270,184; and 5,422,252), transcription-mediated amplification (TMA) (U.S. Patent No. 5,399,491), linked linear amplification (LLA) (U.S. Patent No. 6,027,923), and the like, and isothermal amplification methods such as nucleic acid sequence based amplification (NASBA), and self-sustained sequence replication (Guatelli et al., Proc. Natl. Acad. Sci. USA 87: 1874, 1990). Based

on such methodologies, a person skilled in the art can readily design primers in any suitable regions 5' and 3' to a SNP disclosed herein. Such primers may be used to amplify DNA of any length so long that it contains the SNP of interest in its sequence.

[0075] As used herein, an "amplified polynucleotide" is a SNP-containing nucleic acid molecule whose amount has been increased at least two fold by any nucleic acid amplification method performed *in vitro* as compared to its starting amount in a test sample. In other preferred embodiments, an amplified polynucleotide is the result of at least ten fold, fifty fold, one hundred fold, one thousand fold, or even ten thousand fold increase as compared to its starting amount in a test sample. In a typical PCR amplification, a polynucleotide of interest is often amplified at least fifty thousand fold in amount over the unamplified genomic DNA, but the precise amount of amplification needed for an assay depends on the sensitivity of the subsequent detection method used.

[0076] Generally, an amplified polynucleotide is at least about 16 nucleotides in length. More typically, an amplified polynucleotide is at least about 20 nucleotides in length. In a preferred embodiment an amplified polynucleotide is at least about 30 nucleotides in length. In a more preferred embodiment an amplified polynucleotide is at least about 32, 40, 45, 50, or 60 nucleotides in length. In yet another preferred embodiment, an amplified polynucleotide is at least about 100, 200, or 300 nucleotides in length. While the total length of an amplified polynucleotide described herein can be as long as an exon, an intron or the entire gene where the SNP of interest resides, an amplified product is typically no greater than about 1,000 nucleotides in length (although certain amplification methods may generate amplified products greater than 1000 nucleotides in length). More preferably, an amplified polynucleotide is not greater than about 600 nucleotides in length. It is understood that irrespective of the length of an amplified polynucleotide, a SNP of interest may be located anywhere along its sequence.

[0077] In a specific embodiment, the amplified product is at least about 201 nucleotides in length, comprises one of the transcript-based context sequences or the genomic-based context sequences shown in Tables 1-2. Such a product may have additional sequences on its 5' end or 3' end or both. In another embodiment, the amplified product is about 101 nucleotides in length, and it contains a SNP disclosed herein. Preferably, the SNP is located at the middle of the amplified product (e.g., at position 101 in an amplified product that is 201 nucleotides in length, or at position 51 in an amplified product that is 101 nucleotides in length), or within 1, 2,3,4,5,6,7,8,9,10,12,15, or 20 nucleotides from the middle of the amplified product (however, as indicated above, the SNP of interest may be located anywhere along the length of the amplified product).

[0078] The present invention provides the use of an isolated nucleic acid molecules that comprise, consist of, or consist essentially of one or more polynucleotide sequences that contain the SNP disclosed herein, complements thereof, and SNP-containing fragments thereof in the method of the present invention.

[0079] Accordingly, the present invention provides the use of nucleic acid molecules that consist of any of the nucleotide sequences shown in Table 1 and/or Table 2 (transcript sequence is provided in Table 1 as SEQ ID NO:1 genomic sequence is provided in Table 2 as SEQ ID NO:4 transcript-based SNP context sequence is provided in Table 1 as SEQ ID NO:3 and genomic-based SNP context sequence is provided in Table 2 as SEQ ID NO:5), or any nucleic acid molecule that encodes any of the variant proteins provided in Table 1 (SEQ ID NO:2) in the method of the present invention. A nucleic acid molecule consists of a nucleotide sequence when the nucleotide sequence is the complete nucleotide sequence of the nucleic acid molecule.

[0080] The present invention further provides the use of nucleic acid molecules that consist essentially of any of the nucleotide sequences shown in Table 1 and/or Table 2 (transcript sequence is provided in Table 1 as SEQ ID NO:1, genomic sequence is provided in Table 2 as SEQ ID NO:4, transcript-based SNP context sequence is provided in Table 1 as SEQ ID NO:3, and genomic-based SNP context sequence is provided in Table 2 as SEQ ID NO:5), or any nucleic acid molecule that encodes any of the variant proteins provided in Table 1 (SEQ ID NO:2) in the method of the present invention. A nucleic acid molecule consists essentially of a nucleotide sequence when such a nucleotide sequence is present with only a few additional nucleotide residues in the final nucleic acid molecule.

[0081] The present invention further provides the use of nucleic acid molecules that comprise any of the nucleotide sequences shown in Table 1 and/or Table 2 or a SNP-containing fragment thereof (transcript sequence is provided in Table 1 as SEQ ID NO:1, genomic sequence is provided in Table 2 as SEQ ID NO:4, transcript-based SNP context sequence is provided in Table 1 as SEQ ID NO:3 and genomic-based SNP context sequence is provided in Table 2 as SEQ ID NO:5), or any nucleic acid molecule that encodes any of the variant proteins provided in Table 1 (SEQ ID NO: 2) in the method of the present invention. A nucleic acid molecule comprises a nucleotide sequence when the nucleotide sequence is at least part of the final nucleotide sequence of the nucleic acid molecule. In such a fashion, the nucleic acid molecule can be only the nucleotide sequence or have additional nucleotide residues, such as residues that are naturally associated with it or heterologous nucleotide sequences. Such a nucleic acid molecule can have one to a few additional nucleotides or can comprise many more additional nucleotides. A brief description of how various types of these nucleic acid molecules can be readily made and isolated is provided below, and such techniques are well known to those of ordinary skill in the art (Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, NY).

[0082] The isolated nucleic acid molecules can encode mature proteins plus additional amino or carboxyl-terminal amino acids or both, or amino acids interior to the mature peptide (when the mature form has more than one peptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, facilitate protein trafficking, prolong or shorten protein half-life, or facilitate manipulation of a protein for assay or production. As generally is the case *in situ,* the additional amino acids may be processed away from the mature protein by cellular enzymes.

[0083] Thus, the isolated nucleic acid molecules include, but are not limited to, nucleic acid molecules having a sequence encoding a peptide alone, a sequence encoding a mature peptide and additional coding sequences such as a leader or secretory sequence (e.g., a pre-pro or pro-protein sequence), a sequence encoding a mature peptide with or without additional coding sequences, plus additional non-coding sequences, for example introns and non-coding 5' and 3' sequences such as transcribed but untranslated sequences that play a role in, for example, transcription, mRNA processing (including splicing and polyadenylation signals), ribosome binding, and/or stability of mRNA. In addition, the nucleic acid molecules may be fused to heterologous marker sequences encoding, for example, a peptide that facilitates purification.

[0084] Isolated nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA, which may be obtained, for example, by molecular cloning or produced by chemical synthetic techniques or by a combination thereof (Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, NY). Furthermore, isolated nucleic acid molecules, particularly SNP detection reagents such as probes and primers, can also be partially or completely in the form of one or more types of nucleic acid analogs, such as peptide nucleic acid (PNA) (U.S. Patent Nos. 5,539,082; 5,527,675; 5,623,049; 5,714,331). The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the complementary non-coding strand (anti-sense strand). DNA, RNA, or PNA segments can be assembled, for example, from fragments of the human genome (in the case of DNA or RNA) or single nucleotides, short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic nucleic acid molecule. Nucleic acid molecules can be readily synthesized using the sequences provided herein as a reference; oligonucleotide and PNA oligomer synthesis techniques are well known in the art (see, e.g., Corey, "Peptide nucleic acids: expanding the scope of nucleic acid recognition", Trends Biotechnol. 1997 Jun;15(6):224-9, and Hyrup et al., "Peptide nucleic acids (PNA): synthesis, properties and potential applications", Bioorg Med Chem. 1996 Jan;4(1):5-23). Furthermore, large-scale automated oligonucleotide/PNA synthesis (including synthesis on an array or bead surface or other solid support) can readily be accomplished using commercially available nucleic acid synthesizers, such as the Applied Biosystems (Foster City, CA) 3900 High-Throughput DNA Synthesizer or Expedite 8909 Nucleic Acid Synthesis System, and the sequence information provided herein.

[0085] Described herein are nucleic acid analogs that contain modified, synthetic, or non-naturally occurring nucleotides or structural elements or other alternative/modified nucleic acid chemistries known in the art. Such nucleic acid analogs are useful, for example, as detection reagents (e.g., primers/probes) for detecting SNP identified in Table 1 and/or Table 2. Furthermore, kits/systems (such as beads, arrays, etc.) that include these analogs are also described herein. For example, PNA oligomers that are based on the polymorphic sequences described herein are specifically contemplated. PNA oligomers are analogs of DNA in which the phosphate backbone is replaced with a peptide-like backbone (Lagriffoul et al., Bioorganic & Medicinal Chemistry Letters, 4: 1081-1082 (1994), Petersen et al., Bioorganic & Medicinal Chemistry Letters, 6: 793-796 (1996), Kumar et al., Organic Letters 3(9): 1269-1272 (2001), WO96/04000). PNA hybridizes to complementary RNA or DNA with higher affinity and specificity than conventional oligonucleotides and oligonucleotide analogs. The properties of PNA enable novel molecular biology and biochemistry applications unachievable with traditional oligonucleotides and peptides.

[0086] Additional examples of nucleic acid modifications that improve the binding properties and/or stability of a nucleic acid include the use of base analogs such as inosine, intercalators (U.S. Patent No. 4,835,263) and the minor groove binders (U.S. Patent No. 5,801,115). Thus, references herein to nucleic acid molecules, SNP-containing nucleic acid molecules, SNP detection reagents (e.g., probes and primers), oligonucleotides/polynucleotides include PNA oligomers and other nucleic acid analogs. Other examples of nucleic acid analogs and alternative/modified nucleic acid chemistries known in the art are described in Current Protocols in Nucleic Acid Chemistry, John Wiley & Sons, N.Y. (2002).

[0087] Described herein are nucleic acid molecules that encode fragments of the variant polypeptides disclosed herein as well as nucleic acid molecules that encode obvious variants of such variant polypeptides. Such nucleic acid molecules may be naturally occurring, such as paralogs (different locus) and orthologs (different organism), or may be constructed by recombinant DNA methods or by chemical synthesis. Non-naturally occurring variants may be made by mutagenesis techniques, including those applied to nucleic acid molecules, cells, or organisms. Accordingly, the variants can contain nucleotide substitutions, deletions, inversions and insertions (in addition to the SNP disclosed in Tables 1-2). Variation can occur in either or both the coding and non-coding regions. The variations can produce conservative and/or non-conservative amino acid substitutions.

[0088] Further variants of the nucleic acid molecules disclosed in Tables 1-2, such as naturally occurring allelic variants

(as well as orthologs and paralogs) and synthetic variants produced by mutagenesis techniques, can be identified and/or produced using methods well known in the art. Such further variants can comprise a nucleotide sequence that shares at least 70-80%, 80-85%, 85-90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with a nucleic acid sequence disclosed in Table 1 and/or Table 2 (or a fragment thereof) and that includes the SNP allele disclosed in Table 1 and/or Table 2. Further, variants can comprise a nucleotide sequence that encodes a polypeptide that shares at least 70-80%, 80-85%, 85-90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with a polypeptide sequence disclosed in Table 1 (or a fragment thereof) and that includes the SNP allele disclosed in Table 1 and/or Table 2. Thus, the present invention specifically contemplates the use of isolated nucleic acid molecule that have a certain degree of sequence variation compared with the sequences shown in Tables 1-2, but that contain the SNP allele disclosed herein in the method of the present invention. In other words, as long as an isolated nucleic acid molecule contains the SNP allele disclosed herein, other portions of the nucleic acid molecule that flank the novel SNP allele can vary to some degree from the specific transcript, genomic, and context sequences shown in Tables 1-2, and can encode a polypeptide that varies to some degree from the specific polypeptide sequences shown in Table 1.

[0089] To determine the percent identity of two amino acid sequences or two nucleotide sequences of two molecules that share sequence homology, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% or more of the length of a reference sequence is aligned for comparison purposes. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein, amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

[0090] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. (Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch algorithm (J. Mol. Biol. (48):444-453 (1970)) which has been incorporated into the GAP program in the GCG software package, using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0091] In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (Devereux, J., et al., Nucleic Acids Res. 12(1):387 (1984)), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Myers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4.

[0092] The nucleotide and amino acid sequences described herein can further be used as a "query sequence" to perform a search against sequence databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (J. Mol. Biol. 215:403-10 (1990)). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (Nucleic Acids Res. 25(17):3389-3402 (1997)). When utilizing BLAST and gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. In addition to BLAST, examples of other search and sequence comparison programs used in the art include, but are not limited to, FASTA (Pearson, Methods Mol. Biol. 25, 365-389 (1994)) and KERR (Dufresne et al., Nat Biotechnol 2002 Dec;20(12): 1269-71). For further information regarding bioinformatics techniques, see Current Protocols in Bioinformatics, John Wiley & Sons, Inc., N.Y.

[0093] For reference only, described herein are non-coding fragments of the nucleic acid molecules disclosed in Table 1 and/or Table 2. Preferred non-coding fragments include, but are not limited to, promoter sequences, enhancer sequences, intronic sequences, 5' untranslated regions (UTRs), 3' untranslated regions, gene modulating sequences and gene termination sequences. Such fragments are useful, for example, in controlling heterologous gene expression and in developing screens to identify gene-modulating agents.

SNP Detection Reagents

[0094] In a specific aspect of the present invention, the SNP disclosed in Table 1 and/or Table 2, and their associated transcript sequences (provided in Table 1 as SEQ ID NO:1), genomic sequences (provided in Table 2 as SEQ ID NO: 4), and context sequences (transcript-based context sequences are provided in Table 1 as SEQ ID NO:3; genomic-based context sequence is provided in Table 2 as SEQ ID NO:5), can be used for the design of SNP detection reagents. As used herein, a "SNP detection reagent" is a reagent that specifically detects a specific target SNP position disclosed herein, and that is preferably specific for a particular nucleotide (allele) of the target SNP position (i.e., the detection reagent preferably can differentiate between different alternative nucleotides at a target SNP position, thereby allowing the identity of the nucleotide present at the target SNP position to be determined). Typically, such detection reagent hybridizes to a target SNP-containing nucleic acid molecule by complementary base-pairing in a sequence specific manner, and discriminates the target variant sequence from other nucleic acid sequences such as an art-known form in a test sample. An example of a detection reagent is a probe that hybridizes to a target nucleic acid containing the SNP provided in Table 1 and/or Table 2. In a preferred embodiment, such a probe can differentiate between nucleic acids having a particular nucleotide (allele) at a target SNP position from other nucleic acids that have a different nucleotide at the same target SNP position. In addition, a detection reagent may hybridize to a specific region 5' and/or 3' to a SNP position, particularly a region corresponding to the context sequences provided in Table 1 and/or Table 2 (transcript-based context sequence is provided in Table 1 as SEQ ID NO:3; genomic-based context sequence is provided in Table 2 as SEQ ID NO:5). Another example of a detection reagent is a primer which acts as an initiation point of nucleotide extension along a complementary strand of a target polynucleotide, The SNP sequence information provided herein is also useful for designing primers, e.g. allele-specific primers, to amplify (e.g., using PCR) any SNP disclosed herein.

[0095] In one preferred embodiment, a SNP detection reagent is an isolated or synthetic DNA or RNA polynucleotide probe or primer or PNA oligomer, or a combination of DNA, RNA and/or PNA, that hybridizes to a segment of a target nucleic acid molecule containing the SNP identified in Table 1 and/or Table 2. A detection reagent in the form of a polynucleotide may optionally contain modified base analogs, intercalators or minor groove binders. Multiple detection reagents such as probes may be, for example, affixed to a solid support (e.g., arrays or beads) or supplied in solution (e.g., probe/primer sets for enzymatic reactions such as PCR, RT-PCR, TaqMan assays, or primer-extension reactions) to form a SNP detection kit.

[0096] A probe or primer typically is a substantially purified oligonucleotide or PNA oligomer. Such oligonucleotide typically comprises a region of complementary nucleotide sequence that hybridizes under stringent conditions to at least about 8, 10, 12, 16, 18, 20, 22, 25, 30, 40, 50, 60,100 (or any other number in-between) or more consecutive nucleotides in a target nucleic acid molecule. Depending on the particular assay, the consecutive nucleotides can either include the target SNP position, or be a specific region in close enough proximity 5' and/or 3' to the SNP position to carry out the desired assay.

[0097] Other preferred primer and probe sequences can readily be determined using the transcript sequence (SEQ ID NO:1), genomic sequence (SEQ ID NO:4), and SNP context sequence (transcript-based context sequence is provided in Table 1 as SEQ ID NO:3; genomic-based context sequence is provided in Table 2 as SEQ ID NO:5) disclosed in the Sequence Listing and in Tables 1-2. It will be apparent to one of skill in the art that such primers and probes are directly useful as reagents for genotyping the SNPs of the present invention, and can be incorporated into any kit/system format.

[0098] In order to produce a probe or primer specific for a target SNP-containing sequence, the gene/transcript and/or context sequence surrounding the SNP of interest is typically examined using a computer algorithm which starts at the 5' or at the 3' end of the nucleotide sequence. Typical algorithms will then identify oligomers of defined length that are unique to the gene/SNP context sequence, have a GC content within a range suitable for hybridization, lack predicted secondary structure that may interfere with hybridization, and/or possess other desired characteristics or that lack other undesired characteristics.

[0099] A primer or probe as used in the method of the present invention is typically at least about 8 nucleotides in length. In one embodiment of the invention, a primer or a probe is at least about 10 nucleotides in length. In a preferred embodiment, a primer or a probe is at least about 12 nucleotides in length. In a more preferred embodiment, a primer or probe is at least about 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length. While the maximal length of a probe can be as long as the target sequence to be detected, depending on the type of assay in which it is employed, it is typically less than about 50, 60, 65, or 70 nucleotides in length. In the case of a primer, it is typically less than about 30 nucleotides in length. In a specific preferred embodiment of the invention, a primer or a probe is within the length of about 18 and about 28 nucleotides. However, in other embodiments, such as nucleic acid arrays and other embodiments in which probes are affixed to a substrate, the probes can be longer, such as on the order of 30-70, 75, 80, 90, 100, or more nucleotides in length (see the section below entitled "SNP Detection Kits and Systems").

[0100] For analyzing SNPs, it may be appropriate to use oligonucleotides specific for alternative SNP alleles. Such oligonucleotides which detect single nucleotide variations in target sequences may be referred to by such terms as

"allele-specific oligonucleotides", "allele-specific probes", or "allele-specific primers". The design and use of allele-specific probes for analyzing polymorphisms is described in, e.g., Mutation Detection A Practical Approach, ed. Cotton et al. Oxford University Press, 1998; Saiki et al., Nature 324, 163-166 (1986); Dattagupta, EP235,726; and Saiki, WO 89/11548.

[0101] While the design of each allele-specific primer or probe depends on variables such as the precise composition of the nucleotide sequences flanking a SNP position in a target nucleic acid molecule, and the length of the primer or probe, another factor in the use of primers and probes is the stringency of the condition under which the hybridization between the probe or primer and the target sequence is performed. Higher stringency conditions utilize buffers with lower ionic strength and/or a higher reaction temperature, and tend to require a more perfect match between probe/primer and a target sequence in order to form a stable duplex. If the stringency is too high, however, hybridization may not occur at all. In contrast, lower stringency conditions utilize buffers with higher ionic strength and/or a lower reaction temperature, and permit the formation of stable duplexes with more mismatched bases between a probe/primer and a target sequence. By way of example and not limitation, exemplary conditions for high stringency hybridization conditions using an allele-specific probe are as follows: Prehybridization with a solution containing 5X standard saline phosphate EDTA (SSPE), 0.5% $NaDodSO_4$ (SDS) at 55°C, and incubating probe with target nucleic acid molecules in the same solution at the same temperature, followed by washing with a solution containing 2X SSPE, and 0.1 %SDS at 55°C or room temperature.

[0102] Moderate stringency hybridization conditions may be used for allele-specific primer extension reactions with a solution containing, e.g., about 50mM KCl at about 46°C. Alternatively, the reaction may be carried out at an elevated temperature such as 60°C. In another embodiment, a moderately stringent hybridization condition suitable for oligonucleotide ligation assay (OLA) reactions wherein two probes are ligated if they are completely complementary to the target sequence may utilize a solution of about 100mM KCl at a temperature of 46°C.

[0103] In a hybridization-based assay, allele-specific probes can be designed that hybridize to a segment of target DNA from one individual but do not hybridize to the corresponding segment from another individual due to the presence of different polymorphic forms (e.g., alternative SNP alleles/nucleotides) in the respective DNA segments from the two individuals. Hybridization conditions should be sufficiently stringent that there is a significant detectable difference in hybridization intensity between alleles, and preferably an essentially binary response, whereby a probe hybridizes to only one of the alleles or significantly more strongly to one allele. While a probe may be designed to hybridize to a target sequence that contains a SNP site such that the SNP site aligns anywhere along the sequence of the probe, the probe is preferably designed to hybridize to a segment of the target sequence such that the SNP site aligns with a central position of the probe (e.g., a position within the probe that is at least three nucleotides from either end of the probe). This design of probe generally achieves good discrimination in hybridization between different allelic forms.

[0104] In another embodiment, a probe or primer may be designed to hybridize to a segment of target DNA such that the SNP aligns with either the 5' most end or the 3' most end of the probe or primer. In a specific preferred embodiment which is particularly suitable for use in a oligonucleotide ligation assay (U.S. Patent No. 4,988,617), the 3'most nucleotide of the probe aligns with the SNP position in the target sequence.

[0105] Oligonucleotide probes and primers may be prepared by methods well known in the art. Chemical synthetic methods include, but are limited to, the phosphotriester method described by Narang et al., 1979, Methods in Enzymology 68:90; the phosphodiester method described by Brown et al., 1979, Methods in Enzymology 68:109, the diethylphosphoamidate method described by Beaucage et al., 1981, Tetrahedron Letters 22:1859; and the solid support method described in U.S. Patent No. 4,458,066.

[0106] Allele-specific probes are often used in pairs (or, less commonly, in sets of 3 or 4, such as if a SNP position is known to have 3 or 4 alleles, respectively, or to assay both strands of a nucleic acid molecule for a target SNP allele), and such pairs may be identical except for a one nucleotide mismatch that represents the allelic variants at the SNP position. Commonly, one member of a pair perfectly matches a reference form of a target sequence that has a more common SNP allele (i.e., the allele that is more frequent in the target population) and the other member of the pair perfectly matches a form of the target sequence that has a less common SNP allele (i.e., the allele that is rarer in the target population). In the case of an array, multiple pairs of probes can be immobilized on the same support for simultaneous analysis of multiple different polymorphisms.

[0107] In one type of PCR-based assay, an allele-specific primer hybridizes to a region on a target nucleic acid molecule that overlaps a SNP position and only primes amplification of an allelic form to which the primer exhibits perfect complementarity (Gibbs, 1989, Nucleic Acid Res. 17 2427-2448). Typically, the primer's 3'-most nucleotide is aligned with and complementary to the SNP position of the target nucleic acid molecule. This primer is used in conjunction with a second primer that hybridizes at a distal site. Amplification proceeds from the two primers, producing a detectable product that indicates which allelic form is present in the test sample. A control is usually performed with a second pair of primers, one of which shows a single base mismatch at the polymorphic site and the other of which exhibits perfect complementarity to distal site. The single-base mismatch prevents amplication or substantially reduces amplification efficiency, so that either no detectable product is formed or it is formed in lower amounts or at a slower pace. The method generally works most effectively when the mismatch is at the 3'-most position of the oligonucleotide (i.e., the 3'-most position of the

oligonucleotide aligns with the target SNP position) because this position is most destabilizing to elongation from the primer (see, e.g., WO 93/22456). This PCR-based assay can be utilized as part of the TaqMan assay, described below.

[0108] In a specific embodiment, a primer as used in the method of the invention contains a sequence substantially complementary to a segment of a target SNP-containing nucleic acid molecule except that the primer has a mismatched nucleotide in one of the three nucleotide positions at the 3'-most end of the primer, such that the mismatched nucleotide does not base pair with a particular allele at the SNP site. In a preferred embodiment, the mismatched nucleotide in the primer is the second from the last nucleotide at the 3'-most position of the primer. In a more preferred embodiment, the mismatched nucleotide in the primer is the last nucleotide at the 3'-most position of the primer.

[0109] In another embodiment, a SNP detection reagent as used in the method of the invention is labeled with a fluorogenic reporter dye that emits a detectable signal. While the preferred reporter dye is a fluorescent dye, any reporter dye that can be attached to a detection reagent such as an oligonucleotide probe or primer is suitable for use in the invention. Such dyes include, but are not limited to, Acridine, AMCA, BODIPY, Cascade Blue, Cy2, Cy3, Cy5, Cy7, Dabcyl, Edans, Eosin, Erythrosin, Fluorescein, 6-Fam, Tet, Joe, Hex, Oregon Green, Rhodamine, Rhodol Green, Tamra, Rox, and Texas Red.

[0110] In yet another embodiment, the detection reagent may be further labeled with a quencher dye such as Tamra, especially when the reagent is used as a self-quenching probe such as a TaqMan (U.S. Patent Nos. 5,210,015 and 5,538,848) or Molecular Beacon probe (U.S. Patent Nos. 5,118,801 and 5,312,728), or other stemless or linear beacon probe (Livak et al., 1995, PCR Method Appl. 4:357-362; Tyagi et al., 1996, Nature Biotechnology 14: 303-308; Nazarenko et al., 1997, Nucl. Acids Res. 25:2516-2521; U.S. Patent Nos. 5,866,336 and 6,117,635).

[0111] The detection reagents as used in the method of the invention may also contain other labels, including but not limited to, biotin for streptavidin binding, hapten for antibody binding, and oligonucleotide for binding to another complementary oligonucleotide such as pairs of zipcodes.

[0112] Described herein are reagents that do not contain (or that are complementary to) a SNP nucleotide identified herein but that are used to assay one or more SNPs disclosed herein. For example, primers that flank, but do not hybridize directly to a target SNP position provided herein are useful in primer extension reactions in which the primers hybridize to a region adjacent to the target SNP position (i.e., within one or more nucleotides from the target SNP site). During the primer extension reaction, a primer is typically not able to extend past a target SNP site if a particular nucleotide (allele) is present at that target SNP site, and the primer extension product can readily be detected in order to determine which SNP allele is present at the target SNP site. For example, particular ddNTPs are typically used in the primer extension reaction to terminate primer extension once a ddNTP is incorporated into the extension product (a primer extension product which includes a ddNTP at the 3'-most end of the primer extension product, and in which the ddNTP corresponds to a SNP disclosed herein, is a composition that is described herein). Thus, reagents that bind to a nucleic acid molecule in a region adjacent to a SNP site, even though the bound sequences do not necessarily include the SNP site itself, are also described herein.

SNP Detection Kits and Systems

[0113] A person skilled in the art will recognize that, based on the SNP and associated sequence information disclosed herein, detection reagents can be developed and used to assay any SNP described herein individually or in combination, and such detection reagents can be readily incorporated into one of the established kit or system formats which are well known in the art. The terms "kits" and "systems", as used herein in the context of SNP detection reagents, are intended to refer to such things as combinations of multiple SNP detection reagents, or one or more SNP detection reagents in combination with one or more other types of elements or components (e.g., other types of biochemical reagents, containers, packages such as packaging intended for commercial sale, substrates to which SNP detection reagents are attached, electronic hardware components, etc.). Accordingly, the present invention further provides the use of SNP detection kits and systems, including but not limited to, packaged probe and primer sets (e.g., TaqMan probe/primer sets), arrays/microarrays of nucleic acid molecules, and beads that contain one or more probes, primers, or other detection reagents in the method of the present invention. The kits/systems can optionally include various electronic hardware components; for example, arrays ("DNA chips") and microfluidic systems ("lab-on-a-chip" systems) provided by various manufacturers typically comprise hardware components. Other kits/systems (e.g., probe/primer sets) may not include electronic hardware components, but may be comprised of, for example, one or more SNP detection reagents (along with, optionally, other biochemical reagents) packaged in one or more containers.

[0114] In some embodiments, a SNP detection kit typically contains one or more detection reagents and other components (e.g., a buffer, enzymes such as DNA polymerases or ligases, chain extension nucleotides such as deoxynucleotide triphosphates, and in the case of Sanger-type DNA sequencing reactions, chain terminating nucleotides, positive control sequences, negative control sequences, and the like) necessary to carry out an assay or reaction, such as amplification and/or detection of a SNP-containing nucleic acid molecule. A kit may further contain means for determining the amount of a target nucleic acid, and means for comparing the amount with a standard, and can comprise instructions

for using the kit to detect the SNP-containing nucleic acid molecule of interest. In one embodiment of the present invention, the use of kits is provided which contain the necessary reagents to carry out one or more assays to detect the SNP disclosed herein in the method of the present invention. In a preferred embodiment of the present invention, SNP detection kits/systems are in the form of nucleic acid arrays, or compartmentalized kits, including microfluidic/lab-on-a-chip systems.

[0115] SNP detection kits/systems may contain, for example, one or more probes, or pairs of probes, that hybridize to a nucleic acid molecule at or near each target SNP position. Multiple pairs of allele-specific probes may be included in the kit/system to simultaneously assay large numbers of SNPs, at least one of which is a SNP disclosed herein. In some kits/systems, the allele-specific probes are immobilized to a substrate such as an array or bead. For example, the same substrate can comprise allele-specific probes for detecting at least 1; 10; 100; 1000; 10,000; 100,000 (or any other number in-between) or substantially all of the SNPs disclosed herein.

[0116] The terms "arrays", "microarrays", and "DNA chips" are used herein interchangeably to refer to an array of distinct polynucleotides affixed to a substrate, such as glass, plastic, paper, nylon or other type of membrane, filter, chip, or any other suitable solid support. The polynucleotides can be synthesized directly on the substrate, or synthesized separate from the substrate and then affixed to the substrate. In one embodiment, the microarray is prepared and used according to the methods described in U.S. Patent No. 5,837,832, Chee et al., PCT application W095/11995 (Chee et al.), Lockhart, D. J. et al. (1996; Nat. Biotech. 14: 1675-1680) and Schena, M. et al. (1996; Proc. Natl. Acad. Sci. 93: 10614-10619). In other embodiments, such arrays are produced by the methods described by Brown et al., U.S. Patent No. 5,807,522.

[0117] Nucleic acid arrays are reviewed in the following references: Zammatteo et al., "New chips for molecular biology and diagnostics", Biotechnol Annu Rev. 2002;8:85-101; Sosnowsld et al., "Active microelectronic array system for DNA hybridization, genotyping and pharmacogenomic applications", Psychiatr Genet. 2002 Dec;12(4):181-92; Heller, "DNA microarray technology: devices, systems, and applications", Annu Rev Biomed Eng. 2002;4:129-53. Epub 2002 Mar 22; Kolchinsky et al., "Analysis of SNPs and other genomic variations using gel-based chips", Hum Mutat. 2002 Apr;19 (4):343-60; and McGall et al., "High-density genechip oligonucleotide probe arrays", Adv Biochem Eng Biotechnol. 2002; 77:21-42.

[0118] Any number of probes, such as allele-specific probes, may be implemented in an array, and each probe or pair of probes can hybridize to a different SNP position. In the case of polynucleotide probes, they can be synthesized at designated areas (or synthesized separately and then affixed to designated areas) on a substrate using a light-directed chemical process. Each DNA chip can contain, for example, thousands to millions of individual synthetic polynucleotide probes arranged in a grid-like pattern and miniaturized (e.g., to the size of a dime). Preferably, probes are attached to a solid support in an ordered, addressable array.

[0119] A nucroarray can be composed of a large number of unique, single-stranded polynucleotides; usually either synthetic antisense polynucleotides or fragments of cDNAs, fixed to a solid support. Typical polynucleotides are preferably about 6-60 nucleotides in length, more preferably about 15-30 nucleotides in length, and most preferably about 18-25 nucleotides in length. For certain types of microarrays or other detection kits/systems, it may be preferable to use oligonucleotides that are only about 7-20 nucleotides in length. In other types of arrays, such as arrays used in conjunction with chemiluminescent detection technology, preferred probe lengths can be, for example, about 15-80 nucleotides in length, preferably about 50-70 nucleotides in length, more preferably about 55-65 nucleotides in length, and most preferably about 60 nucleotides in length. The microarray or detection kit can contain polynucleotides that cover the known 5' or 3' sequence of a gene/transcript or target SNP site, sequential polynucleotides that cover the full-length sequence of a gene/transcript; or unique polynucleotides selected from particular areas along the length of a target gene/transcript sequence, particularly areas corresponding to the SNP disclosed in Table 1 and/or Table 2. Polynucleotides used in the microarray or detection kit can be specific to a SNP or SNPs of interest (e.g., specific to a particular SNP allele at a target SNP site, or specific to particular SNP alleles at multiple different SNP sites), or specific to a polymorphic gene/transcript or genes/transcripts of interest

[0120] Hybridization assays based on polynucleotide arrays rely on the differences in hybridization stability of the probes to perfectly matched and mismatched target sequence variants. For SNP genotyping, it is generally preferable that stringency conditions used in hybridization assays are high enough such that nucleic acid molecules that differ from one another at as little as a single SNP position can be differentiated (e.g., typical SNP hybridization assays are designed so that hybridization will occur only if one particular nucleotide is present at a SNP position, but will not occur if an alternative nucleotide is present at that SNP position). Such high stringency conditions may be preferable when using, for example, nucleic acid arrays of allele-specific probes for SNP detection. Such high stringency conditions are described in the preceding section, and are well known to those skilled in the art and can be found in, for example, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6.

[0121] In other embodiments, the arrays are used in conjunction with chemiluminescent detection technology. The following patents and patent applications, provide additional information pertaining to chemiluminescent detection: U.S. patent applications 10/620332 and 10/620333 describe chemiluminescent approaches for microarray detection; U.S. Patent Nos. 6124478, 6107024, 5994073, 5981768, 5871938, 5843681, 5800999, and 5773628 describe methods and

compositions of dioxetane for performing chemiluminescent detection; and U.S. published application US2002/0110828 discloses methods and compositions for microarray controls.

[0122] In one embodiment, a nucleic acid array can comprise an array of probes of about 15-25 nucleotides in length. In further embodiments, a nucleic acid array can comprise any number of probes, in which at least one probe is capable of detecting the SNP disclosed in Table 1 and/or Table 2, and/or at least one probe comprises a fragment of one of the sequences selected from the group consisting of those disclosed in Table 1, Table 2, the Sequence Listing, and sequences complementary thereto, said fragment comprising at least about 8 consecutive nucleotides, preferably 10, 12, 15, 16, 18, 20, more preferably 22, 25, 30, 40, 47, 50, 55, 60, 65, 70, 80, 90, 100, or more consecutive nucleotides (or any other number in-between) and containing (or being complementary to) the SNP allele disclosed in Table 1 and/or Table 2. In some embodiments, the nucleotide complementary to the SNP site is within 5, 4, 3, 2, or 1 nucleotide from the center of the probe, more preferably at the center of said probe.

[0123] A polynucleotide probe can be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application W095/251116 (Baldeschweiler et al.). In another aspect, a "gridded" array analogous to a dot (or slot) blot may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedures. An array, such as those described above, may be produced by hand or by using available devices (slot blot or dot blot apparatus), materials (any suitable solid support), and machines (including robotic instruments), and may contain 8, 24, 96, 384, 1536,6144 or more polynucleotides, or any other number which lends itself to the efficient use of commercially available instrumentation.

[0124] Using such arrays or other kits/systems, the present invention provides methods of identifying the SNP disclosed herein in a test sample. Such methods typically involve incubating a test sample of nucleic acids with an array comprising one or more probes corresponding to at least the SNP position described herein, and assaying for binding of a nucleic acid from the test sample with one or more of the probes. Conditions for incubating a SNP detection reagent (or a kit/system that employs one or more such SNP detection reagents) with a test sample vary. Incubation conditions depend on such factors as the format employed in the assay, the detection methods employed, and the type and nature of the detection reagents used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification and array assay formats can readily be adapted to detect the SNPs disclosed herein.

[0125] A SNP detection kit/system as used in the method of the present invention may include components that are used to prepare nucleic acids from a test sample for the subsequent amplification and/or detection of a SNP-containing nucleic acid molecule. Such sample preparation components can be used to produce nucleic acid extracts (including DNA and/or RNA), proteins or membrane extracts from any bodily fluids (such as blood, serum, plasma, urine, saliva, phlegm, gastric juices, semen, tears, sweat, etc.), skin, hair, cells (especially nucleated cells), biopsies, buccal swabs or tissue specimens. The test samples used in the above-described methods will vary based on such factors as the assay format, nature of the detection method, and the specific tissues, cells or extracts used as the test sample to be assayed. Methods of preparing nucleic acids, proteins, and cell extracts are well known in the art and can be readily adapted to obtain a sample that is compatible with the system utilized. Automated sample preparation systems for extracting nucleic acids from a test sample are commercially available, and examples are Qiagen's BioRobot 9600, Applied Biosystems' PRISM 6700, and Roche Molecular Systems' COBAS AmpliPrep System.

[0126] Another form of kit disclosed herein is a compartmentalized kit. A compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include, for example, small glass containers, plastic containers, strips of plastic, glass or paper, or arraying material such as silica. Such containers allow one to efficiently transfer reagents from one compartment to another compartment such that the test samples and reagents are not cross-contaminated, or from one container to another vessel not included in the kit, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another or to another vessel. Such containers may include, for example, one or more containers which will accept the test sample, one or more containers which contain at least one probe or other SNP detection reagent for detecting one or more SNPs disclosed herein, one or more containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and one or more containers which contain the reagents used to reveal the presence of the bound probe or other SNP detection reagents. The kit can optionally further comprise compartments and/or reagents for, for example, nucleic acid amplification or other enzymatic reactions such as primer extension reactions, hybridization, ligation, electrophoresis (preferably capillary electrophoresis), mass spectrometry, and/or laser-induced fluorescent detection. The kit may also include instructions for using the kit. Exemplary compartmentalized kits include microfluidic devices known in the art (see, e.g., Weigl et al., "Lab-on-a-chip for drug development", Adv Drug Deliv Rev. 2003 Feb 24;55(3):349-77). In such microfluidic devices, the containers may be referred to as, for example, microfluidic "compartments", "chambers", or "channels".

[0127] Microfluidic devices, which may also be referred to as "lab-on-a-chip" systems, biomedical micro-electro-mechanical systems (bioMEMs), or multicomponent integrated systems, are exemplary kits/systems of the present invention for analyzing SNPs. Such systems miniaturize and compartmentalize processes such as probe/target hybridization, nucleic acid amplification, and capillary electrophoresis reactions in a single functional device. Such microfluidic devices

typically utilize detection reagents in at least one aspect of the system, and such detection reagents may be used to detect one or more SPNs disclosed herein. One example of a microfluidic system is disclosed in U.S. Patent No. 5,589,136, which describes the integration of PCR amplification and capillary electrophoresis in chips. Exemplary microfluidic systems comprise a pattern of microchannels designed onto a glass, silicon, quartz, or plastic wafer included on a microchip. The movements of the samples may be controlled by electric, electroosmotic or hydrostatic forces applied across different areas of the microchip to create functional microscopic valves and pumps with no moving parts. Varying the voltage can be used as a means to control the liquid flow at intersections between the micro-machined channels and to change the liquid flow rate for pumping across different sections of the microchip. See, for example, U.S. Patent Nos. 6,153,073, Dubrow et al., and 6,156,181, Parce et al.

[0128] For genotyping SNPs, an exemplary microfluidic system may integrate, for example, nucleic acid amplification, primer extension, capillary electrophoresis, and a detection method such as laser induced fluorescence detection. In a first step of an exemplary process for using such an exemplary system, nucleic acid samples are amplified, preferably by PCR. Then, the amplification products are subjected to automated primer extension reactions using ddNTPs (specific fluorescence for each ddNTP) and the appropriate oligonucleotide primers to carry out primer extension reactions which hybridize just upstream of the targeted SNP. Once the extension at the 3' end is completed, the primers are separated from the unincorporated fluorescent ddNTPs by capillary electrophoresis. The separation medium used in capillary electrophoresis can be, for example, polyacrylamide, polyethyleneglycol or dextran. The incorporated ddNTPs in the single nucleotide primer extension products are identified by laser-induced fluorescence detection. Such an exemplary microchip can be used to process, for example, at least 96 to 384 samples, or more, in parallel.

USES OF NUCLEIC ACID MOLECULES

[0129] The nucleic acid molecules as used in the method of the present invention have a variety of uses, especially in the diagnosis and treatment of myocardial infarction. For example, the nucleic acid molecules are useful as hybridization probes, such as for genotyping SNPs in messenger RNA, transcript, cDNA, genomic DNA, amplified DNA or other nucleic acid molecules, and for isolating full-length cDNA and genomic clones encoding the variant peptides disclosed in Table 1 as well as their orthologs.

[0130] A probe can hybridize to any nucleotide sequence along the entire length of a nucleic acid molecule provided in Table 1 and/or Table 2. Preferably, a probe as used in the method of the present invention hybridizes to a region of a target sequence that encompasses the SNP position indicated in Table 1 and/or Table 2. More preferably, a probe hybridizes to a SNP-containing target sequence in a sequence-specific manner such that it distinguishes the target sequence from other nucleotide sequences which vary from the target sequence only by which nucleotide is present at the SNP site. Such a probe is particularly useful for detecting the presence of a SNP-containing nucleic acid in a test sample, or for determining which nucleotide (allele) is present at a particular SNP site (i.e., genotyping the SNP site).

[0131] A nucleic acid hybridization probe may be used for determining the presence, level, form, and/or distribution of nucleic acid expression. The nucleic acid whose level is determined can be DNA or RNA. Accordingly, probes specific for the SNPs described herein can be used to assess the presence, expression and/or gene copy number in a given cell, tissue, or organism. These uses are relevant for diagnosis of disorders involving an increase or decrease in gene expression relative to normal levels. *In vitro* techniques for detection of mRNA include, for example, Northern blot hybridizations and *in situ* hybridizations. *In vitro* techniques for detecting DNA include Southern blot hybridizations and *in situ* hybridizations (Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY).

[0132] Probes can be used as part of a diagnostic test kit for identifying cells or tissues in which a variant protein is expressed, such as by measuring the level of a variant protein-encoding nucleic acid (e.g., mRNA) in a sample of cells from a subject or determining if a polynucleotide contains a SNP of interest.

[0133] Thus, the nucleic acid molecules disclosed herein can be used in the method of the present invention as hybridization probes to detect the SNPs disclosed herein, thereby determining whether an individual with the polymorphisms is at risk for myocardial infarction or has developed early stage myocardial infarction. Detection of a SNP associated with a disease phenotype provides a diagnostic tool for an active disease and/or genetic predisposition to the disease.

[0134] The nucleic acid molecules described herein are also useful as primers to amplify any given region of a nucleic acid molecule, particularly a region containing a SNP identified in Table 1 and/or Table 2.

[0135] The nucleic acid molecules described herein are also useful for constructing recombinant vectors (described in greater detail below). Such vectors include expression vectors that express a portion of, or all of, any of the variant peptide sequences provided in Table 1. Vectors also include insertion vectors, used to integrate into another nucleic acid molecule sequence, such as into the cellular genome, to alter *in situ* expression of a gene and/or gene product. For example, an endogenous coding sequence can be replaced via homologous recombination with all or part of the coding region containing one or more specifically introduced SNPs.

[0136] The nucleic acid molecules described herein are also useful for expressing antigenic portions of the variant proteins, particularly antigenic portions that contain a variant amino acid sequence (e.g., an amino acid substitution) caused by the SNP disclosed in Table 1 and/or Table 2.

[0137] The nucleic acid molecules described herein are also useful for constructing vectors containing a gene regulatory region of the nucleic acid molecules described herein.

[0138] The nucleic acid molecules described herein are also useful for designing ribozymes corresponding to all, or a part, of an mRNA molecule expressed from a SNP-containing nucleic acid molecule described herein.

[0139] The nucleic acid molecules described herein are also useful for constructing host cells expressing a part, or all, of the nucleic acid molecules and variant peptides.

[0140] The nucleic acid molecules described herein are also useful for constructing transgenic animals expressing all, or a part, of the nucleic acid molecules and variant peptides. The production of recombinant cells and transgenic animals having nucleic acid molecules which contain the SNP disclosed in Table 1 and/or Table 2 allow, for example, effective clinical design of treatment compounds and dosage regimens.

[0141] The nucleic acid molecules described herein are also useful in assays for drug screening to identify compounds that, for example, modulate nucleic acid expression.

[0142] The nucleic acid molecules described herein are also useful in gene therapy in patients whose cells have aberrant gene expression. Thus, recombinant cells, which include a patient's cells that have been engineered *ex vivo* and returned to the patient, can be introduced into an individual where the recombinant cells produce the desired protein to treat the individual.

SNP Genotyping Methods

[0143] The process of determining which specific nucleotide (i.e., allele) is present at each of one or more SNP positions, such as the SNP position in a nucleic acid molecule disclosed in Table 1 and/or Table 2, is referred to as SNP genotyping. The present invention provides methods of SNP genotyping, such as for use in screening for myocardial infarction or related pathologies, or determining predisposition thereto, or determining responsiveness to a form of treatment, or in genome mapping or SNP association analysis, etc.

[0144] Nucleic acid samples can be genotyped to determine which allele(s) is/are present at any given genetic region (e.g., SNP position) of interest by methods well known in the art. The neighboring sequence can be used to design SNP detection reagents such as oligonucleotide probes, which may optionally be implemented in a kit format. Exemplary SNP genotyping methods are described in Chen et al., "Single nucleotide polymorphism genotyping: biochemistry, protocol, cost and throughput", Pharmacogenomics J. 2003;3(2):77-96; Kwok et al., "Detection of single nucleotide polymorphisms", Curr Issues Mol Biol. 2003 Apr;5 (2):43-60; Shi, "Technologies for individual genotyping: detection of genetic polymorphisms in drug targets and disease genes", Am J Pharmacogenomics. 2002;2(3):197-205; and Kwok, "Methods for genotyping single nucleotide polymorphisms", Annu Rev Genomics Hum Genet 2001;2:235-58. Exemplary techniques for high-throughput SNP genotyping are described in Mamellos, "High-throughput SNP analysis for genetic association studies", Curr Opin Drug Discov Devel. 2003 May;6(3):317-21. Common SNP genotyping methods include, but are not limited to, TaqMan assays, molecular beacon assays, nucleic acid arrays, allele-specific primer extension, allele-specific PCR, arrayed primer extension, homogeneous primer extension assays, primer extension with detection by mass spectrometry, pyrosequencing, multiplex primer extension sorted on genetic arrays, ligation with rolling circle amplification, homogeneous ligation, OLA (U.S. Patent No. 4,988,167), multiplex ligation reaction sorted on genetic arrays, restriction-fragment length polymorphism, single base extension-tag assays, and the Invader assay. Such methods may be used in combination with detection mechanisms such as, for example, luminescence or chemiluminescence detection, fluorescence detection, time-resolved fluorescence detection, fluorescence resonance energy transfer, fluorescence polarization, mass spectrometry, and electrical detection.

[0145] Various methods for detecting polymorphisms include, but are not limited to, methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA duplexes (Myers et al., Science 230: 1242 (1985); Cotton et al., PNAS 85:4397 (1988); and Saleeba et al., Meth. Enzymol. 217:286-295 (1992)), comparison of the electrophoretic mobility of variant and wild type nucleic acid molecules (Orita et al., PNAS 86:2766 (1989); Cotton et al., Mutat. Res. 285:125-144 (1993); and Hayashi et al., Genet. Anal. Tech. Appl. 9:73-79 (1992)), and assaying the movement of polymorphic or wild-type fragments in polyacrylamide gels containing a gradient of denaturant using denaturing gradient gel electrophoresis (DGGE) (Myers et al., Nature 313:495 (1985)). Sequence variations at specific locations can also be assessed by nuclease protection assays such as RNase and S1 protection or chemical cleavage methods.

[0146] In a preferred embodiment, SNP genotyping is performed using the TaqMan assay, which is also known as the 5' nuclease assay (U.S. Patent Nos. 5,210,015 and 5,538,848). The TaqMan assay detects the accumulation of a specific amplified product during PCR. The TaqMan assay utilizes an oligonucleotide probe labeled with a fluorescent reporter dye and a quencher dye. The reporter dye is excited by irradiation at an appropriate wavelength, it transfers

energy to the quencher dye in the same probe via a process called fluorescence resonance energy transfer (FRET). When attached to the probe, the excited reporter dye does not emit a signal. The proximity of the quencher dye to the reporter dye in the intact probe maintains a reduced fluorescence for the reporter. The reporter dye and quencher dye may be at the 5' most and the 3' most ends, respectively, or vice versa. Alternatively, the reporter dye may be at the 5' or 3' most end while the quencher dye is attached to an internal nucleotide, or vice versa. In yet another embodiment, both the reporter and the quencher may be attached to internal nucleotides at a distance from each other such that fluorescence of the reporter is reduced.

[0147] During PCR, the 5' nuclease activity of DNA polymerase cleaves the probe, thereby separating the reporter dye and the quencher dye and resulting in increased fluorescence of the reporter. Accumulation of PCR product is detected directly by monitoring the increase in fluorescence of the reporter dye. The DNA polymerase cleaves the probe between the reporter dye and the quencher dye only if the probe hybridizes to the target SNP-containing template which is amplified during PCR, and the probe is designed to hybridize to the target SNP site only if a particular SNP allele is present.

[0148] Preferred TaqMan primer and probe sequences can readily be determined using the SNP and associated nucleic acid sequence information provided herein. A number of computer programs, such as Primer Express (Applied Biosystems, Foster City, CA), can be used to rapidly obtain optimal primer/probe sets. It will be apparent to one of skill in the art that such primers and probes for detecting the SNPs described herein are useful in diagnostic assays for myocardial infarction and related pathologies, and can be readily incorporated into a kit format. The present invention also includes modifications of the Taqman assay well known in the art such as the use of Molecular Beacon probes (U.S. Patent Nos. 5,118,801 and 5,312,728) and other variant formats (U.S. Patent Nos. 5,866,336 and 6,117,635).

[0149] Another preferred method for genotyping the SNPs described herein is the use of two oligonucleotide probes in an OLA (see, e.g., U.S. Patent No. 4,988,617). In this method, one probe hybridizes to a segment of a target nucleic acid with its 3' most end aligned with the SNP site. A second probe hybridizes to an adjacent segment of the target nucleic acid molecule directly 3' to the first probe. The two juxtaposed probes hybridize to the target nucleic acid molecule, and are ligated in the presence of a linking agent such as a ligase if there is perfect complementarity between the 3' most nucleotide of the first probe with the SNP site. If there is a mismatch, ligation would not occur. After the reaction, the ligated probes are separated from the target nucleic acid molecule, and detected as indicators of the presence of a SNP.

[0150] The following patents, patent applications, and published international patent applications, provide additional information pertaining to techniques for carrying out various types of OLA: U.S. Patent Nos. 6027889, 6268148, 5494810, 5830711, and 6054564 describe OLA strategies for performing SNP detection; WO 97/31256 and WO 00/56927 describe OLA strategies for performing SNP detection using universal arrays, wherein a zipcode sequence can be introduced into one of the hybridization probes, and the resulting product, or amplified product, hybridized to a universal zip code array; U.S. application US01/17329 (and 09/584,905) describes OLA (or LDR) followed by PCR, wherein zipcodes are incorporated into OLA probes, and amplified PCR products are determined by electrophoretic or universal zipcode array readout; U.S. applications 60/427818, 60/445636, and 60/445494 describe SNPlex methods and software for multiplexed SNP detection using OLA followed by PCR, wherein zipcodes are incorporated into OLA probes, and amplified PCR products are hybridized with a zipchute reagent, and the identity of the SNP determined from electrophoretic readout of the zipchute. In some embodiments, OLA is carried out prior to PCR (or another method of nucleic acid amplification). In other embodiments, PCR (or another method of nucleic acid amplification) is carried out prior to OLA.

[0151] Another method for SNP genotyping is based on mass spectrometry. Mass spectrometry takes advantage of the unique mass of each of the four nucleotides of DNA. SNPs can be unambiguously genotyped by mass spectrometry by measuring the differences in the mass of nucleic acids having alternative SNP alleles. MALDI-TOF (Matrix Assisted Laser Desorption Ionization - Time of Flight) mass spectrometry technology is preferred for extremely precise determinations of molecular mass, such as SNPs. Numerous approaches to SNP analysis have been developed based on mass spectrometry. Preferred mass spectrometry-based methods of SNP genotyping include primer extension assays, which can also be utilized in combination with other approaches, such as traditional gel-based formats and microarrays.

[0152] Typically, the primer extension assay involves designing and annealing a primer to a template PCR amplicon upstream (5') from a target SNP position. A mix of dideoxynucleotide triphosphates (ddNTPs) and/or deoxynucleotide triphosphates (dNTPs) are added to a reaction mixture containing template (e.g., a SNP-containing nucleic acid molecule which has typically been amplified, such as by PCR), primer, and DNA polymerase. Extension of the primer terminates at the first position in the template where a nucleotide complementary to one of the ddNTPs in the mix occurs. The primer can be either immediately adjacent (i.e., the nucleotide at the 3' end of the primer hybridizes to the nucleotide next to the target SNP site) or two or more nucleotides removed from the SNP position. If the primer is several nucleotides removed from the target SNP position, the only limitation is that the template sequence between the 3' end of the primer and the SNP position cannot contain a nucleotide of the same type as the one to be detected, or this will cause premature termination of the extension primer. Alternatively, if all four ddNTPs alone, with no dNTPs, are added to the reaction mixture, the primer will always be extended by only one nucleotide, corresponding to the target SNP position. In this

instance, primers are designed to bind one nucleotide upstream from the SNP position (i.e., the nucleotide at the 3' end of the primer hybridizes to the nucleotide that is immediately adjacent to the target SNP site on the 5' side of the target SNP site). Extension by only one nucleotide is preferable, as it minimizes the overall mass of the extended primer, thereby increasing the resolution of mass differences between alternative SNP nucleotides. Furthermore, mass-tagged ddNTPs can be employed in the primer extension reactions in place of unmodified ddNTPs. This increases the mass difference between primers extended with these ddNTPs, thereby providing increased sensitivity and accuracy, and is particularly useful for typing heterozygous base positions. Mass-tagging also alleviates the need for intensive sample-preparation procedures and decreases the necessary resolving power of the mass spectrometer.

[0153] The extended primers can then be purified and analyzed by MALDI-TOF mass spectrometry to determine the identity of the nucleotide present at the target SNP position. In one method of analysis, the products from the primer extension reaction are combined with light absorbing crystals that form a matrix. The matrix is then hit with an energy source such as a laser to ionize and desorb the nucleic acid molecules into the gas-phase. The ionized molecules are then ejected into a flight tube and accelerated down the tube towards a detector. The time between the ionization event, such as a laser pulse, and collision of the molecule with the detector is the time of flight of that molecule. The time of flight is precisely correlated with the mass-to-charge ratio (m/z) of the ionized molecule. Ions with smaller m/z travel down the tube faster than ions with larger m/z and therefore the lighter ions reach the detector before the heavier ions. The time-of-flight is then converted into a corresponding, and highly precise, m/z. In this manner, SNPs can be identified based on the slight differences in mass, and the corresponding time of flight differences, inherent in nucleic acid molecules having different nucleotides at a single base position. For further information regarding the use of primer extension assays in conjunction with MALDI-TOF mass spectrometry for SNP genotyping, see, e.g., Wise et al., "A standard protocol for single nucleotide primer extension in the human genome using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry", Rapid Commun Mass Spectrom. 2003;17(11):1195-202.

[0154] The following references provide further information describing mass spectrometry-based methods for SNP genotyping: Bocker, "SNP and mutation discovery using base-specific cleavage and MALDI-TOF mass spectrometry", Bioinformatics. 2003 Jul; 19 Suppl 1:I44-I53; Storm et al., "MALDI-TOF mass spectrometry-based SNP genotyping", Methods Mol Biol. 2003;212:241-62; Jurinke et al., "The use of MassARRAY technology for high throughput genotyping", Adv Biochem Eng Biotechnol. 2002;77:57-74; and Jurinke et al., "Automated genotyping using the DNA MassArray technology", Methods Mol Biol. 2002;187:179-92.

[0155] SNPs can also be scored by direct DNA sequencing. A variety of automated sequencing procedures can be utilized ((1995) Biotechniques 19:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO94/16101; Cohen et al., Adv. Chromatogr. 36:127-162 (1996); and Griffin et al., Appl. Biochem. Biotechnol. 38:147-159 (1993)). The nucleic acid sequences described herein enable one of ordinary skill in the art to readily design sequencing primers for such automated sequencing procedures. Commercial instrumentation, such as the Applied Biosystems 377, 3100,3700,3730, and 3730x1 DNA Analyzers (Foster City, CA), is commonly used in the art for automated sequencing.

[0156] Other methods that can be used to genotype the SNPs described herein include single-strand conformational polymorphism (SSCP), and denaturing gradient gel electrophoresis (DGGE) (Myers et al., Nature 313:495 (1985)). SSCP identifies base differences by alteration in electrophoretic migration of single stranded PCR products, as described in Orita et al., Proc. Nat. Acad. Single-stranded PCR products can be generated by heating or otherwise denaturing double stranded PCR products. Single-stranded nucleic acids may refold or form secondary structures that are partially dependent on the base sequence. The different electrophoretic mobilities of single-stranded amplification products are related to base-sequence differences at SNP positions. DGGE differentiates SNP alleles based on the different sequence-dependent stabilities and melting properties inherent in polymorphic DNA and the corresponding differences in electrophoretic migration patterns in a denaturing gradient gel (Erlich, ed., PCR Technology, Principles and Applications for DNA Amplification, W.H. Freeman and Co, New York, 1992, Chapter 7).

[0157] Sequence-specific ribozymes (U.S.Patent No. 5,498,531) can also be used to score SNPs based on the development or loss of a ribozyme cleavage site. Perfectly matched sequences can be distinguished from mismatched sequences by nuclease cleavage digestion assays or by differences in melting temperature. If the SNP affects a restriction enzyme cleavage site, the SNP can be identified by alterations in restriction enzyme digestion patterns, and the corresponding changes in nucleic acid fragment lengths determined by gel electrophoresis

[0158] SNP genotyping can include the steps of, for example, collecting a biological sample from a human subject (e.g., sample of tissues, cells, fluids, secretions, etc.), isolating nucleic acids (e.g., genomic DNA, mRNA or both) from the cells of the sample, contacting the nucleic acids with one or more primers which specifically hybridize to a region of the isolated nucleic acid containing a target SNP under conditions such that hybridization and amplification of the target nucleic acid region occurs, and determining the nucleotide present at the SNP position of interest, or, in some assays, detecting the presence or absence of an amplification product (assays can be designed so that hybridization and/or amplification will only occur if a particular SNP allele is present or absent). In some assays, the size of the amplification product is detected and compared to the length of a control sample; for example, deletions and insertions can be detected

by a change in size of the amplified product compared to a normal genotype.

[0159] SNP genotyping is useful for numerous practical applications, as described below. Examples of such applications include, but are not limited to, SNP-disease association analysis, disease predisposition screening, disease diagnosis, disease prognosis, disease progression monitoring, determining therapeutic strategies based on an individual's genotype ("pharmacogenomics"), developing therapeutic agents based on SNP genotypes associated with a disease or likelihood of responding to a drug, stratifying a patient population for clinical trial for a treatment regimen, predicting the likelihood that an individual will experience toxic side effects from a therapeutic agent, and human identification applications such as forensics.

Analysis of Genetic Association Between SNPs and Phenotypic Traits

[0160] SNP genotyping for disease diagnosis, disease predisposition screening, disease prognosis, determining drug responsiveness (pharmacogenomics), drug toxicity screening, and other uses described herein, typically relies on initially establishing a genetic association between one or more specific SNPs and the particular phenotypic traits of interest.

[0161] Different study designs may be used for genetic association studies (Modem Epidemiology, Lippincott Williams & Wilkins (1998), 609-622). Observational studies are most frequently carried out in which the response of the patients is not interfered with. The first type of observational study identifies a sample of persons in whom the suspected cause of the disease is present and another sample of persons in whom the suspected cause is absent, and then the frequency of development of disease in the two samples is compared. These sampled populations are called cohorts, and the study is a prospective study. The other type of observational study is case-control or a retrospective study. In typical case-control studies, samples are collected from individuals with the phenotype of interest (cases) such as certain manifestations of a disease, and from individuals without the phenotype (controls) in a population (target population) that conclusions are to be drawn from. Then the possible causes of the disease are investigated retrospectively. As the time and costs of collecting samples in case-control studies are considerably less than those for prospective studies, case-control studies are the more commonly used study design in genetic association studies, at least during the exploration and discovery stage.

[0162] In both types of observational studies, there may be potential confounding factors that should be taken into consideration. Confounding factors are those that are associated with both the real cause(s) of the disease and the disease itself, and they include demographic information such as age, gender, ethnicity as well as environmental factors. When confounding factors are not matched in cases and controls in a study, and are not controlled properly, spurious association results can arise. If potential confounding factors are identified, they should be controlled for by analysis methods explained below.

[0163] In a genetic association study, the cause of interest to be tested is a certain allele or a SNP or a combination of alleles or a haplotype from several SNPs. Thus, tissue specimens (e.g., whole blood) from the sampled individuals may be collected and genomic DNA genotyped for the SNP(s) of interest. In addition to the phenotypic trait of interest, other information such as demographic (e.g., age, gender, ethnicity, etc.), clinical, and environmental information that may influence the outcome of the trait can be collected to further characterize and define the sample set. In many cases, these factors are known to be associated with diseases and/or SNP allele frequencies. There are likely gene-environment and/or gene-gene interactions as well. Analysis methods to address gene-environment and gene-gene interactions (for example, the effects of the presence of both susceptibility alleles at two different genes can be greater than the effects of the individual alleles at two genes combined) are discussed below.

[0164] After all the relevant phenotypic and genotypic information has been obtained, statistical analyses are carried out to determine if there is any significant correlation between the presence of an allele or a genotype with the phenotypic characteristics of an individual. Preferably, data inspection and cleaning are first performed before carrying out statistical tests for genetic association. Epidemiological and clinical data of the samples can be summarized by descriptive statistics with tables and graphs. Data validation is preferably performed to check for data completion, inconsistent entries, and outliers. Chi-squared tests and t-tests (Wilcoxon rank-sum tests if distributions are not normal) may then be used to check for significant differences between cases and controls for discrete and continuous variables, respectively. To ensure genotyping quality, Hardy-Weinberg disequilibrium tests can be performed on cases and controls separately. Significant deviation from Hardy-Weinberg equilibrium (HWE) in both cases and controls for individual markers can be indicative of genotyping errors. If HWE is violated in a majority of markers, it is indicative of population substructure that should be further investigated. Moreover, Hardy-Weinberg disequilibrium in cases only can indicate genetic association of the markers with the disease (Genetic Data Analysis, Weir B., Sinauer (1990)).

[0165] To test whether an allele of a single SNP is associated with the case or control status of a phenotypic trait, one skilled in the art can compare allele frequencies in cases and controls. Standard chi-squared tests and Fisher exact tests can be carried out on a 2x2 table (2 SNP alleles x 2 outcomes in the categorical trait of interest). To test whether genotypes of a SNP are associated, chi-squared tests can be carried out on a 3x2 table (3 genotypes x 2 outcomes). Score tests are also carried out for genotypic association to contrast the three genotypic frequencies (major homozygotes,

heterozygotes and minor homozygotes) in cases and controls, and to look for trends using 3 different modes of inheritance, namely dominant (with contrast coefficients 2, -1, -1), additive (with contrast coefficients 1, 0, -1) and recessive (with contrast coefficients 1, 1, -2). Odds ratios for minor versus major alleles, and odds ratios for heterozygote and homozygote variants versus the wild type genotypes are calculated with the desired confidence limits, usually 95%.

[0166] In order to control for confounders and to test for interaction and effect modifiers, stratified analyses may be performed using stratified factors that are likely to be confounding, including demographic information such as age, ethnicity, and gender, or an interacting element or effect modifier, such as a known major gene (e.g., APOE for Alzheimer's disease or HLA genes for autoimmune diseases), or environmental factors such as smoking in lung cancer. Stratified association tests may be carried out using Cochran-Mantel-Haenszel tests that take into account the ordinal nature of genotypes with 0, 1, and 2 variant alleles. Exact tests by StatXact may also be performed when computationally possible. Another way to adjust for confounding effects and test for interactions is to perform stepwise multiple logistic regression analysis using statistical packages such as SAS or R. Logistic regression is a model-building technique in which the best fitting and most parsimonious model is built to describe the relation between the dichotomous outcome (for instance, getting a certain disease or not) and a set of independent variables (for instance, genotypes of different associated genes, and the associated demographic and environmental factors). The most common model is one in which the logit transformation of the odds ratios is expressed as a linear combination of the variables (main effects) and their cross-product terms (interactions) (Applied Logistic Regression, Hosmer and Lemeshow, Wiley (2000)). To test whether a certain variable or interaction is significantly associated with the outcome, coefficients in the model are first estimated and then tested for statistical significance of their departure from zero.

[0167] In addition to performing association tests one marker at a time, haplotype association analysis may also be performed to study a number of markers that are closely linked together. Haplotype association tests can have better power than genotypic or allelic association tests when the tested markers are not the disease-causing mutations themselves but are in linkage disequilibrium with such mutations. The test will even be more powerful if the disease is indeed caused by a combination of alleles on a haplotype (e.g., APOE is a haplotype formed by 2 SNPs that are very close to each other). In order to perform haplotype association effectively, marker-marker linkage disequilibrium measures, both D' and R^2, are typically calculated for the markers within a gene to elucidate the haplotype structure. Recent studies (Daly et al, Nature Genetics, 29, 232-235, 2001) in linkage disequilibrium indicate that SNPs within a gene are organized in block pattern, and a high degree of linkage disequilibrium exists within blocks and very little linkage disequilibrium exists between blocks. Haplotype association with the disease status can be performed using such blocks once they have been elucidated.

[0168] Haplotype association tests can be carried out in a similar fashion as the allelic and genotypic association tests. Each haplotype in a gene is analogous to an allele in a multi-allelic marker. One skilled in the art can either compare the haplotype frequencies in cases and controls or test genetic association with different pairs of haplotypes. It has been proposed (Schaid et al, Am. J. Hum. Genet., 70, 425-434, 2002) that score tests can be done on haplotypes using the program "haplo.score". In that method, haplotypes are first inferred by EM algorithm and score tests are carried out with a generalized linear model (GLM) framework that allows the adjustment of other factors.

[0169] An important decision in the performance of genetic association tests is the determination of the significance level at which significant association can be declared when the p-value of the tests reaches that level. In an exploratory analysis where positive hits will be followed up in subsequent confirmatory testing, an unadjusted p-value <0.1 (a significance level on the lenient side) may be used for generating hypotheses for significant association of a SNP with certain phenotypic characteristics of a disease. It is preferred that a p-value < 0.05 (a significance level traditionally used in the art) is achieved in order for a SNP to be considered to have an association with a disease. It is more preferred that a p-value <0.01 (a significance level on the stringent side) is achieved for an association to be declared. When hits are followed up in confirmatory analyses in more samples of the same source or in different samples from different sources, adjustment for multiple testing will be performed as to avoid excess number of hits while maintaining the experiment-wise error rates at 0.05. While there are different methods to adjust for multiple testing to control for different kinds of error rates, a commonly used but rather conservative method is Bonferroni correction to control the experiment-wise or family-wise error rate (Multiple comparisons and multiple tests, Westfall et al, SAS Institute (1999)). Permutation tests to control for the false discovery rates, FDR, can be more powerful (Benjamini and Hochberg, Journal of the Royal Statistical Society, Series B 57, 1289-1300, 1995, Resampling-based Multiple Testing, Westfall and Young, Wiley (1993)). Such methods to control for multiplicity would be preferred when the tests are dependent and controlling for false discovery rates is sufficient as opposed to controlling for the experiment-wise error rates.

[0170] In replication studies using samples from different populations after statistically significant markers have been identified in the exploratory stage, meta-analyses can then be performed by combining evidence of different studies (Modern Epidemiology, Lippincott Williams & Wilkins, 1998, 643-673). If available, association results known in the art for the same SNPs can be included in the meta-analyses.

[0171] Since both genotyping and disease status classification can involve errors, sensitivity analyses may be performed to see how odds ratios and p-values would change upon various estimates on genotyping and disease classifi-

cation error rates.

[0172] It has been well known that subpopulation-based sampling bias between cases and controls can lead to spurious results in case-control association studies (Ewens and Spielman, Am. J. Hum. Genet. 62, 450-458, 1995) when prevalence of the disease is associated with different subpopulation groups. Such bias can also lead to a loss of statistical power in genetic association studies. To detect population stratification, Pritchard and Rosenberg (Pritchard et al. Am. J. Hum. Gen. 1999, 65:220-228) suggested typing markers that are unlinked to the disease and using results of association tests on those markers to determine whether there is any population stratification. When stratification is detected, the genomic control (GC) method as proposed by Devlin and Roeder (Devlin et al. Biometrics 1999, 55:997-1004) can be used to adjust for the inflation of test statistics due to population stratification. GC method is robust to changes in population structure levels as well as being applicable to DNA pooling designs (Devlin et al. Genet. Epidem. 20001, 21: 273-284).

[0173] While Pritchard's method recommended using 15-20 unlinked microsatellite markers, it suggested using more than 30 biallelic markers to get enough power to detect population stratification. For the GC method, it has been shown (Bacanu et al. Am. J. Hum. Genet. 2000, 66:1933-1944) that about 60-70 biallelic markers are sufficient to estimate the inflation factor for the test statistics due to population stratification. Hence, 70 intergenic SNPs can be chosen in unlinked regions as indicated in a genome scan (Kehoe et al. Hum. Mol. Genet. 1999, 8:237-245).

[0174] Once individual risk factors, genetic or non-genetic, have been found for the predisposition to disease, the next step is to set up a classification/prediction scheme to predict the category (for instance, disease or no-disease) that an individual will be in depending on his genotypes of associated SNPs and other non-genetic risk factors. Logistic regression for discrete trait and linear regression for continuous trait are standard techniques for such tasks (Applied Regression Analysis, Draper and Smith, Wiley (1998)). Moreover, other techniques can also be used for setting up classification. Such techniques include, but are not limited to, MART, CART, neural network, and discriminant analyses that are suitable for use in comparing the performance of different methods (The Elements of Statistical Learning, Hastie, Tibshirani & Friedman, Springer (2002)).

Disease Diagnosis and Predisposition Screening

[0175] Information on association/correlation between genotypes and disease-related phenotypes can be exploited in several ways. For example, in the case of a highly statistically significant association between one or more SNPs with predisposition to a disease for which treatment is available, detection of such a genotype pattern in an individual may justify immediate administration of treatment, or at least the institution of regular monitoring of the individual. Detection of the susceptibility alleles associated with serious disease in a couple contemplating having children may also be valuable to the couple in their reproductive decisions. In the case of a weaker but still statistically significant association between a SNP and a human disease, immediate therapeutic intervention or monitoring may not be justified after detecting the susceptibility allele or SNP. Nevertheless, the subject can be motivated to begin simple life-style changes (e.g., diet, exercise) that can be accomplished at little or no cost to the individual but would confer potential benefits in reducing the risk of developing conditions for which that individual may have an increased risk by virtue of having the susceptibility allele(s).

[0176] The SNPs described herein may contribute to myocardial infarction in an individual in different ways. Some polymorphisms occur within a protein coding sequence and contribute to disease phenotype by affecting protein structure. Other polymorphisms occur in noncoding regions but may exert phenotypic effects indirectly via influence on, for example, replication, transcription, and/or translation. A single SNP may affect more than one phenotypic trait. Likewise, a single phenotypic trait may be affected by multiple SNPs in different genes.

[0177] As used herein, the terms "diagnose", "diagnosis", and "diagnostics" include, but are not limited to any of the following: detection of myocardial infarction that an individual may presently have or be at risk for, predisposition screening (i.e., determining the increased risk for an individual in developing myocardial infarction in the future, or determining whether an individual has a decreased risk of developing myocardial infarction in the future; in the case of recurrent myocardial infarction (RMI), predisposition screening may typically involve determining the risk that an individual who has previously had a myocardial infarction will develop another myocardial infarction in the future, or determining whether an individual who has not experienced a myocardial infarction will be at risk for developing recurrent myocardial infarctions in the future), determining a particular type or subclass of myocardial infarction in an individual known to have myocardial infarction, confirming or reinforcing a previously made diagnosis of myocardial infarction, pharmacogenomic evaluation of an individual to determine which therapeutic strategy that individual is most likely to positively respond to or to predict whether a patient is likely to respond to a particular treatment, predicting whether a patient is likely to experience toxic effects from a particular treatment or therapeutic compound, and evaluating the future prognosis of an individual having myocardial infarction. Such diagnostic uses are based on the SNPs individually or in a unique combination or SNP haplotypes described herein.

[0178] Haplotypes are particularly useful in that, for example, fewer SNPs can be genotyped to determine if a particular

genomic region harbors a locus that influences a particular phenotype, such as in linkage disequilibrium-based SNP association analysis.

[0179] Linkage disequilibrium (LD) refers to the co-inheritance of alleles (e.g., alternative nucleotides) at two or more different SNP sites at frequencies greater than would be expected from the separate frequencies of occurrence of each allele in a given population. The expected frequency of co-occurrence of two alleles that are inherited independently is the frequency of the first allele multiplied by the frequency of the second allele. Alleles that co-occur at expected frequencies are said to be in "linkage equilibrium". In contrast, LD refers to any non-random genetic association between allele(s) at two or more different SNP sites, which is generally due to the physical proximity of the two loci along a chromosome. LD can occur when two or more SNPs sites are in close physical proximity to each other on a given chromosome and therefore alleles at these SNP sites will tend to remain unseparated for multiple generations with the consequence that a particular nucleotide (allele) at one SNP site will show a non-random association with a particular nucleotide (allele) at a different SNP site located nearby. Hence, genotyping one of the SNP sites will give almost the same information as genotyping the other SNP site that is in LD.

[0180] For diagnostic purposes, if a particular SNP site is found to be useful for diagnosing myocardial infarction, then the skilled artisan would recognize that other SNP sites which are in LD with this SNP site would also be useful for diagnosing the condition. Various degrees of LD can be encountered between two or more SNPs with the result being that some SNPs are more closely associated (i.e., in stronger LD) than others. Furthermore, the physical distance over which LD extends along a chromosome differs between different regions of the genome, and therefore the degree of physical separation between two or more SNP sites necessary for LD to occur can differ between different regions of the genome.

[0181] For diagnostic applications, polymorphisms (e.g., SNPs and/or haplotypes) that are not the actual disease-causing (causative) polymorphisms, but are in LD with such causative polymorphisms, are also useful. In such instances, the genotype of the polymorphism(s) that is/are in LD with the causative polymorphism is predictive of the genotype of the causative polymorphism and, consequently, predictive of the phenotype (e.g., myocardial infarction) that is influenced by the causative SNP(s). Thus, polymorphic markers that are in LD with causative polymorphisms are useful as diagnostic markers, and are particularly useful when the actual causative polymorphism(s) is/are unknown.

[0182] Linkage disequilibrium in the human genome is reviewed in: Wall et al., "Haplotype blocks and linkage disequilibrium in the human genome", Nat Rev Genet. 2003 Aug;4(8):587-97; Garner et al., "On selecting markers for association studies: patterns of linkage disequilibrium between two and three diallelic loci", Genet Epidemiol. 2003 Jan; 24(1):57-67; Ardlie et al., "Patterns of linkage disequilibrium in the human genome", Nat Rev Genet. 2002 Apr;3(4): 299-309 (erratum in Nat Rev Genet 2002 Jul;3(7):566); and Remm et al., "High-density genotyping and linkage disequilibrium in the human genome using chromosome 22 as a model"; Curr Opin Chem Biol. 2002 Feb;6(1):24-30.

[0183] The contribution or association of particular SNPs and/or SNP haplotypes with disease phenotypes, such as myocardial infarction, enables the SNPs described herein to be used to develop superior diagnostic tests capable of identifying individuals who express a detectable trait, such as myocardial infarction, as the result of a specific genotype, or individuals whose genotype places them at an increased or decreased risk of developing a detectable trait at a subsequent time as compared to individuals who do not have that genotype. As described herein, diagnostics may be based on a single SNP or a group of SNPs. Combined detection of a plurality of SNPs (for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 24, 25, 30, 32, 48, 50, 64, 96, 100, or any other number in-between, or more, of the SNPs described herein typically increases the probability of an accurate diagnosis. For example, the presence of a single SNP known to correlate with myocardial infarction might indicate a probability of 20% that an individual has or is at risk of developing myocardial infarction, whereas detection of five SNPs, each of which correlates with myocardial infarction, might indicate a probability of 80% that an individual has or is at risk of developing myocardial infarction. To further increase the accuracy of diagnosis or predisposition screening, analysis of the SNPs described herein can be combined with that of other polymorphisms or other risk factors of myocardial infarction, such as disease symptoms, pathological characteristics, family history, diet, environmental factors or lifestyle factors.

[0184] It will, of course, be understood by practitioners skilled in the treatment or diagnosis of myocardial infarction that the present invention generally does not intend to provide an absolute identification of individuals who are at risk (or less at risk) of developing myocardial infarction, and/or pathologies related to myocardial infarction, but rather to indicate a certain increased (or decreased) degree or likelihood of developing the disease based on statistically significant association results. However, this information is extremely valuable as it can be used to, for example, initiate preventive treatments or to allow an individual carrying one or more significant SNPs or SNP haplotypes to foresee warning signs such as minor clinical symptoms, or to have regularly scheduled physical exams to monitor for appearance of a condition in order to identify and begin treatment of the condition at an early stage. Particularly with diseases that are extremely debilitating or fatal if not treated on time, the knowledge of a potential predisposition, even if this predisposition is not absolute, would likely contribute in a very significant manner to treatment efficacy.

[0185] The diagnostic techniques described herein may employ a variety of methodologies to determine whether a test subject has a SNP or a SNP pattern associated with an increased or decreased risk of developing a detectable trait

or whether the individual suffers from a detectable trait as a result of a particular polymorphism/mutation, including, for example, methods which enable the analysis of individual chromosomes for haplotyping, family studies, single sperm DNA analysis, or somatic hybrids. The trait analyzed using the diagnostics of the invention may be any detectable trait that is commonly observed in pathologies and disorders related to myocardial infarction.

[0186] Another aspect of the present invention relates to a method of determining whether an individual is at risk (or less at risk) of developing one or more traits or whether an individual expresses one or more traits as a consequence of possessing a particular trait-causing or trait-influencing allele. These methods generally involve obtaining a nucleic acid sample from an individual and assaying the nucleic acid sample to determine which nucleotide(s) is/are present at one or more SNP positions, wherein the assayed nucleotide(s) is/are indicative of an increased or decreased risk of developing the trait or indicative that the individual expresses the trait as a result of possessing a particular trait-causing or trait-influencing allele.

[0187] In another embodiment, the SNP detection reagents described herein are used to determine whether an individual has one or more SNP allele(s) affecting the level (e.g., the concentration of mRNA or protein in a sample, etc.) or pattern (e.g., the kinetics of expression, rate of decomposition, stability profile, Km, Vmax, etc.) of gene expression (collectively, the "gene response" of a cell or bodily fluid). Such a determination can be accomplished by screening for mRNA or protein expression (e.g., by using nucleic acid arrays, RT-PCR, TaqMan assays, or mass spectrometry), identifying genes having altered expression in an individual, genotypin the SNP disclosed in Table 1 and/or Table 2 that could affect the expression of the genes having altered expression (e.g., SNPs that are in and/or around the gene(s) having altered expression, SNPs in regulatory/control regions, SNPs in and/or around other genes that are involved in pathways that could affect the expression of the gene(s) having altered expression, or all SNPs could be genotyped), and correlating SNP genotypes with altered gene expression. In this manner, specific SNP alleles at particular SNP sites can be identified that affect gene expression.

Pharmacogenomics and Therapeutics/Drug Development

[0188] For reference only, disclosed herein are methods for assessing the pharmacogenomics of a subject harboring particular SNP alleles or haplotypes to a particular therapeutic agent or pharmaceutical compound, or to a class of such compounds. Pharmacogenomics deals with the roles which clinically significant hereditary variations (e.g., SNPs) play in the response to drugs due to altered drug disposition and/or abnormal action in affected persons. See, e.g., Roses, Nature 405, 857-865 (2000); Gould Rothberg, Nature Biotechnology 19, 209-211 (2001); Eichelbaum, Clip. Exp. Pharmocol. Physiol. 23(10-11):983-985 (1996); and Linder, Clin. Chem. 43(2):254-266 (1997). The clinical outcomes of these variations can result in severe toxicity of therapeutic drugs in certain individuals or therapeutic failure of drugs in certain individuals as a result of individual variation in metabolism. Thus, the SNP genotype of an individual can determine the way a therapeutic compound acts on the body or the way the body metabolizes the compound. For example, SNPs in drug metabolizing enzymes can affect the activity of these enzymes, which in turn can affect both the intensity and duration of drug action, as well as drug metabolism and clearance.

[0189] The discovery of SNPs in drug metabolizing enzymes, drug transporters, proteins for pharmaceutical agents, and other drug targets has explained why some patients do not obtain the expected drug effects, show an exaggerated drug effect, or experience serious toxicity from standard drug dosages. SNPs can be expressed in the phenotype of the extensive metabolizer and in the phenotype of the poor metabolizer. Accordingly, SNPs may lead to allelic variants of a protein in which one or more of the protein functions in one population are different from those in another population. SNPs and the encoded variant peptides thus provide targets to ascertain a genetic predisposition that can affect treatment modality. For example, in a ligand-based treatment, SNPs may give rise to amino terminal extracellular domains and/or other ligand-binding regions of a receptor that are more or less active in ligand binding, thereby affecting subsequent protein activation. Accordingly, ligand dosage would necessarily be modified to maximize the therapeutic effect within a given population containing particular SNP alleles or haplotypes.

[0190] As an alternative to genotyping, specific variant proteins containing variant amino acid sequences encoded by alternative SNP alleles could be identified. Thus, pharmacogenomic characterization of an individual permits the selection of effective compounds and effective dosages of such compounds for prophylactic or therapeutic uses based on the individual's SNP genotype, thereby enhancing and optimizing the effectiveness of the therapy. Furthermore, the production of recombinant cells and transgenic animals containing particular SNPs/haplotypes allow effective clinical design and testing of treatment compounds and dosage regimens. For example, transgenic animals can be produced that differ only in specific SNP alleles in a gene that is orthologous to a human disease susceptibility gene.

[0191] Pharmacogenomic uses of the SNPs described herein provide several significant advantages for patient care, particularly in treating myocardial infarction. Pharmacogenomic characterization of an individual, based on an individual's SNP genotype, can identify those individuals unlikely to respond to treatment with a particular medication and thereby allows physicians to avoid prescribing the ineffective medication to those individuals. On the other hand, SNP genotyping of an individual may enable physicians to select the appropriate medication and dosage regimen that will be most effective

based on an individual's SNP genotype. This information increases a physician's confidence in prescribing medications and motivates patients to comply with their drug regimens. Furthermore, pharmacogenomics may identify patients predisposed to toxicity and adverse reactions to particular drugs or drug dosages. Adverse drug reactions lead to more than 100,000 avoidable deaths per year in the United States alone and therefore represent a significant cause of hospitalization and death, as well as a significant economic burden on the healthcare system (Pfost et. al., Trends in Biotechnology, Aug. 2000.). Thus, pharmacogenomics based on the SNPs disclosed herein has the potential to both save lives and reduce healthcare costs substantially.

[0192] Pharmacogenomics in general is discussed further in Rose et al., "Pharmacogenetic analysis of clinically relevant genetic polymorphisms", Methods Mol Med. 2003;85:225-37. Pharmacogenomics as it relates to Alzheimer's disease and other neurodegenerative disorders is discussed in Cacabelos, "Pharmacogenomics for the treatment of dementia", Ann Med. 2002;34(5):357-79, Maimone et al., "Pharmacogenomics of neurodegenerative diseases", Eur J Pharmacol. 2001 Feb 9;413(1):11-29, and Poirier, "Apolipoprotein E: a pharmacogenetic target for the treatment of Alzheimer's disease", Mol Diagn. 1999 Dec;4(4):335-41. Pharmacogenomics as it relates to cardiovascular disorders is discussed in Siest et al., "Pharmacogenomics of drugs affecting the cardiovascular system", Clin Chem Lab Med. 2003 Apr;41(4):590-9, Mukherjee et al., "Pharmacogenomics in cardiovascular diseases", Prog Cardiovasc Dis. 2002 May-Jun;44(6):479-98, and Mooser et al., "Cardiovascular pharmacogenetics in the SNP era", J Thromb Haemost. 2003 Jul;1(7):1398-402. Pharmacogenomics as it relates to cancer is discussed in McLeod et al., "Cancer pharmacogenomics: SNPs, chips, and the individual patient". Cancer Invest. 2003;21(4):630-40 and Watters et al., "Cancer pharmacogenomics: current and future applications", Biochim Biophys Acta. 2003 Mar 17;1603(2):99-111.

[0193] The SNPs described herein also can be used to identify novel therapeutic targets for myocardial infarction. For example, genes containing the disease-associated variants ("variant genes") or their products, as well as genes or their products that are directly or indirectly regulated by or interacting with these variant genes or their products, can be targeted for the development of therapeutics that, for example, treat the disease or prevent or delay disease onset. The therapeutics may be composed of, for example, small molecules, proteins, protein fragments or peptides, antibodies, nucleic acids, or their derivatives or mimetics which modulate the functions or levels of the target genes or gene products.

[0194] The SNP-containing nucleic acid molecules disclosed herein, and their complementary nucleic acid molecules, may be used as antisense constructs to control gene expression in cells, tissues, and organisms. Antisense technology is well established in the art and extensively reviewed in Antisense Drug Technology: Principles, Strategies, and Applications, Crooke (ed.), Marcel Dekker, Inc.: New York (2001). An antisense nucleic acid molecule is generally designed to be complementary to a region of mRNA expressed by a gene so that the antisense molecule hybridizes to the mRNA and thereby blocks translation of mRNA into protein. Various classes of antisense oligonucleotides are used in the art, two of which are cleavers and blockers. Cleavers, by binding to target RNAs, activate intracellular nucleases (e.g., RNaseH or RNase L) that cleave the target RNA. Blockers, which also bind to target RNAs, inhibit protein translation through steric hindrance of ribosomes. Exemplary blockers include peptide nucleic acids, morpholinos, locked nucleic acids, and methylphosphonates (see, e.g., Thompson, Drug Discovery Today, 7 (17): 912-917 (2002)). Antisense oligonucleotides are directly useful as therapeutic agents, and are also useful for determining and validating gene function (e.g., in gene knock-out or knock-down experiments).

[0195] Antisense technology is further reviewed in: Lavery et al., "Antisense and RNAi: powerful tools in drug target discovery and validation", Curr Opin Drug Discov Devel. 2003 Jul;6(4):561-9; Stephens et al., "Antisense oligonucleotide therapy in cancer", Curr Opin Mol Ther. 2003 Apr;5(2):118-22; Kurreck, "Antisense technologies. Improvement through novel chemical modifications", Eur J Biochem. 2003 Apr;270(8):1628-44; Dias et al., "Antisense oligonucleotides: basic concepts and mechanisms", Mol Cancer Ther. 2002 Mar;1(5):347-55; Chen, "Clinical development of antisense oligonucleotides as anti-cancer therapeutics", Methods Mol Med. 2003;75:621-36; Wang et al., "Antisense anticancer oligonucleotide therapeutics", Curr Cancer Drug Targets. 2001 Nov;1(3):177-96; and Bennett, "Efficiency of antisense oligonucleotide drug discovery", Antisense Nucleic Acid Drug Dev. 2002 Jun;12(3):215-24.

[0196] The SNPs described herein are particularly useful for designing antisense reagents that are specific for particular nucleic acid variants. Based on the SNP information disclosed herein, antisense oligonucleotides can be produced that specifically target mRNA molecules that contain one or more particular SNP nucleotides. In this manner, expression of mRNA molecules that contain one or more undesired polymorphisms (e.g., SNP nucleotides that lead to a defective protein such as an amino acid substitution in a catalytic domain) can be inhibited or completely blocked. Thus, antisense oligonucleotides can be used to specifically bind a particular polymorphic form (e.g., a SNP allele that encodes a defective protein), thereby inhibiting translation of this form, but which do not bind an alternative polymorphic form (e.g., an alternative SNP nucleotide that encodes a protein having normal function).

[0197] Antisense molecules can be used to inactivate mRNA in order to inhibit gene expression and production of defective proteins. Accordingly, these molecules can be used to treat a disorder, such as myocardial infarction, characterized by abnormal or undesired gene expression or expression of certain defective proteins. This technique can involve cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Possible mRNA regions include, for example, protein-coding

regions and particularly protein-coding regions corresponding to catalytic activities, substrate ligand binding, or other functional activities of a protein.

[0198] The SNPs described herein are also useful for designing RNA interference reagents that specifically target nucleic acid molecules having particular SNP variants. RNA interference (RNAi), also referred to as gene silencing, is based on using double-stranded RNA (dsRNA) molecules to turn genes off. When introduced into a cell, dsRNAs are processed by the cell into short fragments (generally about 21-22bp in length) known as small interfering RNAs (siRNAs) which the cell uses in a sequence-specific manner to recognize and destroy complementary RNAs (Thompson, Drug Discovery Today, 7 (17): 912-917 (2002)). Thus, because RNAi molecules, including siRNAs, act in a sequence-specific manner, the SNPs described herein can be used to design RNAi reagents that recognize and destroy nucleic acid molecules having specific SNP alleles/nucleotides (such as deleterious alleles that lead to the production of defective proteins), while not affecting nucleic acid molecules having alternative SNP alleles (such as alleles that encode proteins having normal function). As with antisense reagents, RNAi reagents may be directly useful as therapeutic agents (e.g., for turning off defective, disease-causing genes), and are also useful for characterizing and validating gene function (e.g., in gene knock-out or knock-down experiments).

[0199] The following references provide a further review of RNAi: Agami, "RNAi and related mechanisms and their potential use for therapy", Curr Opin Chem Biol. 2002 Dec;6(6):829-34; Lavery et al., "Antisense and RNAi: powerful tools in drug target discovery and validation", Curr Opin Drug Discov Devel. 2003 Jul;6(4):561-9; Shi, "Mammalian RNAi for the masses", Trends Genet 2003 Jan;19(1):9-12), Shuey et al., "RNAi: gene-silencing in therapeutic intervention", Drug Discovery Today 2002 Oct;7(20):1040-1046; McManus et al., Nat Rev Genet 2002 Oct;3(10):737-47; Xia et al., Nat Biotechnol 2002 Oct;20(10):1006-10; Plasterk et al., Curr Opin Genet Dev 2000 Oct;10(5):562-7; Bosher et al., Nat Cell Biol 2000 Feb;2(2):E31-6; and Hunter, Curr Biol 1999 Jun 17;9(12):R440-2).

[0200] A subject suffering from a pathological condition, such as myocardial infarction, ascribed to a SNP may be treated so as to correct the genetic defect (see Kren et al., Proc. Natl. Acad. Sci. USA 96:10349-10354 (1999)). Such a subject can be identified by any method that can detect the polymorphism in a biological sample drawn from the subject. Such a genetic defect may be permanently corrected by administering to such a subject a nucleic acid fragment incorporating a repair sequence that supplies the normal/wild-type nucleotide at the position of the SNP. This site-specific repair sequence can encompass an RNA/DNA oligonucleotide that operates to promote endogenous repair of a subject's genomic DNA. The site-specific repair sequence is administered in an appropriate vehicle, such as a complex with polyethylenimine, encapsulated in anionic liposomes, a viral vector such as an adenovirus, or other pharmaceutical composition that promotes intracellular uptake of the administered nucleic acid. A genetic defect leading to an inborn pathology may then be overcome, as the chimeric oligonucleotides induce incorporation of the normal sequence into the subject's genome. Upon incorporation, the normal gene product is expressed, and the replacement is propagated, thereby engendering a permanent repair and therapeutic enhancement of the clinical condition of the subject.

[0201] In cases in which a cSNP results in a variant protein that is ascribed to be the cause of, or a contributing factor to, a pathological condition, a method of treating such a condition can include administering to a subject experiencing the pathology the wild-type/normal cognate of the variant protein. Once administered in an effective dosing regimen, the wild-type cognate provides complementation or remediation of the pathological condition.

[0202] For reference only, described is a method for identifying a compound or agent that can be used to treat myocardial infarction. The SNPs disclosed herein are useful as targets for the identification and/or development of therapeutic agents. A method for identifying a therapeutic agent or compound typically includes assaying the ability of the agent or compound to modulate the activity and/or expression of a SNP-containing nucleic acid or the encoded product and thus identifying an agent or a compound that can be used to treat a disorder characterized by undesired activity or expression of the SNP-containing nucleic acid or the encoded product. The assays can be performed in cell-based and cell-free systems. Cell-based assays can include cells naturally expressing the nucleic acid molecules of interest or recombinant cells genetically engineered to express certain nucleic acid molecules.

[0203] Variant gene expression in a myocardial infarction patient can include, for example, either expression of a SNP-containing nucleic acid sequence (for instance, a gene that contains a SNP can be transcribed into an mRNA transcript molecule containing the SNP, which can in turn be translated into a variant protein) or altered expression of a normal/wild-type nucleic acid sequence due to one or more SNPs (for instance, a regulatory/control region can contain a SNP that affects the level or pattern of expression of a normal transcript).

[0204] Assays for variant gene expression can involve direct assays of nucleic acid levels (e.g., mRNA levels), expressed protein levels, or of collateral compounds involved in a signal pathway. Further, the expression of genes that are up- or down-regulated in response to the signal pathway can also be assayed. In this embodiment, the regulatory regions of these genes can be operably linked to a reporter gene such as luciferase.

[0205] Modulators of variant gene expression can be identified in a method wherein, for example, a cell is contacted with a candidate compound/agent and the expression of mRNA determined. The level of expression of mRNA in the presence of the candidate compound is compared to the level of expression of mRNA in the absence of the candidate compound. The candidate compound can then be identified as a modulator of variant gene expression based on this

comparison and be used to treat a disorder such as myocardial infarction that is characterized by variant gene expression (e.g., either expression of a SNP-containing nucleic acid or altered expression of a normal/wild-type nucleic acid molecule due to one or more SNPs that affect expression of the nucleic acid molecule) due to one or more SNPs described herein. When expression of mRNA is statistically significantly greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of nucleic acid expression. When nucleic acid expression is statistically significantly less in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of nucleic acid expression.

[0206] For reference only, described are methods of treatment, with the SNP or associated nucleic acid domain (e.g., catalytic domain, ligand/substrate-binding domain, regulatory/control region, etc.) or gene, or the encoded mRNA transcript, as a target, using a compound identified through drug screening as a gene modulator to modulate variant nucleic acid expression. Modulation can include either up-regulation (i.e., activation or agonization) or down-regulation (i.e., suppression or antagonization) of nucleic acid expression.

[0207] Expression of mRNA transcripts and encoded proteins, either wild type or variant, may be altered in individuals with a particular SNP allele in a regulatory/control element, such as a promoter or transcription factor binding domain, that regulates expression. In this situation, methods of treatment and compounds can be identified, as discussed herein, that regulate or overcome the variant regulatory/control element, thereby generating normal, or healthy, expression levels of either the wild type or variant protein.

[0208] The SNP-containing nucleic acid molecules described herein are also useful for monitoring the effectiveness of modulating compounds on the expression or activity of a variant gene, or encoded product, in clinical trials or in a treatment regimen. Thus, the gene expression pattern can serve as an indicator for the continuing effectiveness of treatment with the compound, particularly with compounds to which a patient can develop resistance, as well as an indicator for toxicities. The gene expression pattern can also serve as a marker indicative of a physiological response of the affected cells to the compound. Accordingly, such monitoring would allow either increased administration of the compound or the administration of alternative compounds to which the patient has not become resistant. Similarly, if the level of nucleic acid expression falls below a desirable level, administration of the compound could be commensurately decreased.

[0209] In another aspect, there is provided a pharmaceutical pack comprising a therapeutic agent (e.g., a small molecule drug, antibody, peptide, antisense or RNAi nucleic acid molecule, etc.) and a set of instructions for administration of the therapeutic agent to humans diagnostically tested for one or more SNPs or SNP haplotypes described herein.

[0210] The SNPs/haplotypes described herein are also useful for improving many different aspects of the drug development process. For example, individuals can be selected for clinical trials based on their SNP genotype. Individuals with SNP genotypes that indicate that they are most likely to respond to the drug can be included in the trials and those individuals whose SNP genotypes indicate that they are less likely to or would not respond to the drug, or suffer adverse reactions, can be eliminated from the clinical trials. This not only improves the safety of clinical trials, but also will enhance the chances that the trial will demonstrate statistically significant efficacy. Furthermore, the SNPs described herein may explain why certain previously developed drugs performed poorly in clinical trials and may help identify a subset of the population that would benefit from a drug that had previously performed poorly in clinical trials, thereby "rescuing" previously developed drugs, and enabling the drug to be made available to a particular myocardial infarction patient population that can benefit from it.

[0211] SNPs have many important uses in drug discovery, screening, and development. A high probability exists that, for any gene/protein selected as a potential drug target, variants of that gene/protein will exist in a patient population. Thus, determining the impact of gene/protein variants on the selection and delivery of a therapeutic agent should be an integral aspect of the drug discovery and development process. (Jazwinska, A Trends Guide to Genetic Variation and Genomic Medicine, 2002 Mar; S30-S36).

[0212] Knowledge of variants (e.g., SNPs and any corresponding amino acid polymorphisms) of a particular therapeutic target (e.g., a gene, mRNA transcript, or protein) enables parallel screening of the variants in order to identify therapeutic candidates (e.g., small molecule compounds, antibodies, antisense or RNAi nucleic acid compounds, etc.) that demonstrate efficacy across variants (Rothberg, Nat Biotechnol 2001 Mar;19(3):209-11). Such therapeutic candidates would be expected to show equal efficacy across a larger segment of the patient population, thereby leading to a larger potential market for the therapeutic candidate.

[0213] Furthermore, identifying variants of a potential therapeutic target enables the most common form of the target to be used for selection of therapeutic candidates, thereby helping to ensure that the experimental activity that is observed for the selected candidates reflects the real activity expected in the largest proportion of a patient population (Jazwinska, A Trends Guide to Genetic Variation and Genomic Medicine, 2002 Mar; S30-S36).

[0214] Additionally, screening therapeutic candidates against all known variants of a target can enable the early identification of potential toxicities and adverse reactions relating to particular variants. For example, variability in drug absorption, distribution, metabolism and excretion (ADME) caused by, for example, SNPs in therapeutic targets or drug metabolizing genes, can be identified, and this information can be utilized during the drug development process to

minimize variability in drug disposition and develop therapeutic agents that are safer across a wider range of a patient population. The SNPs described herein, including the variant proteins and encoding polymorphic nucleic acid molecules provided in Tables 1-2, are useful in conjunction with a variety of toxicology methods established in the art, such as those set forth in Current Protocols in Toxicology, John Wiley & Sons, Inc., N.Y.

[0215] Furthermore, therapeutic agents that target any art-known proteins (or nucleic acid molecules, either RNA or DNA) may cross-react with the variant proteins (or polymorphic nucleic acid molecules) disclosed in Table 1, thereby significantly affecting the pharmacokinetic properties of the drug. Consequently, the protein variants and the SNP-containing nucleic acid molecules disclosed in Tables 1-2 are useful in developing, screening, and evaluating therapeutic agents that target corresponding art-known protein forms (or nucleic acid molecules). Additionally, as discussed above, knowledge of all polymorphic forms of a particular drug target enables the design of therapeutic agents that are effective against most or all such polymorphic forms of the drug target.

Pharmaceutical Compositions and Administration Thereof

[0216] Any of the myocardial infarction-associated proteins, and encoding nucleic acid molecules, disclosed herein can be used as therapeutic targets (or directly used themselves as therapeutic compounds) for treating myocardial infarction and related pathologies, and the present disclosure enables therapeutic compounds (e.g., small molecules, antibodies, therapeutic proteins, RNAi and antisense molecules, etc.) to be developed that target (or are comprised of) any of these therapeutic targets.

[0217] In general, a therapeutic compound will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the therapeutic compound described herein, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

[0218] Therapeutically effective amounts of therapeutic compounds may range from, for example, approximately 0.01-50 mg per kilogram body weight of the recipient per day; preferably about 0.1-20 mg/kg/day. Thus, as an example, for administration to a 70 kg person, the dosage range would most preferably be about 7 mg to 1.4 g per day.

[0219] In general, therapeutic .compounds will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal, or by suppository), or parenteral (e.g., intramuscular, intravenous, or subcutaneous) administration. The preferred manner of administration is oral or parenteral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Oral compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

[0220] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills, or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area, i.e., decreasing particle size. For example, U.S. Patent No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a cross-linked matrix of macromolecules. U.S. Patent No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[0221] Pharmaceutical compositions are comprised of, in general, a therapeutic compound in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the therapeutic compound. Such excipients may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one skilled in the art.

[0222] Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

[0223] Compressed gases may be used to disperse a compound described herein in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[0224] Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

[0225] The amount of the therapeutic compound in a formulation can vary within the full range employed by those skilled in the art Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of the therapeutic compound based on the total formulation, with the balance being one or more suitable pharmaceutical

excipients. Preferably, the compound is present at a level of about 1-80 wt %.

[0226] Therapeutic compounds can be administered alone or in combination with other therapeutic compounds or in combination with one or more other active ingredient(s). For example, an inhibitor or stimulator of a myocardial infarction-associated protein can be administered in combination with another agent that inhibits or stimulates the activity of the same or a different myocardial infarction-associated protein to thereby counteract the affects of myocardial infarction.

[0227] For further information regarding pharmacology, see Current Protocols in Pharmacology, John Wiley & Sons, Inc., N.Y.

Human Identification Applications

[0228] For reference only, in addition to their diagnostic and therapeutic uses in myocardial infarction and related pathologies, the SNPs described herein are also useful as human identification markers for such applications as forensics, paternity testing, and biometrics (see, e.g., Gill, "An assessment of the utility of single nucleotide polymorphisms (SNPs) for forensic purposes", Int J Legal Med. 2001;114(4-5):204-10). Genetic variations in the nucleic acid sequences between individuals can be used as genetic markers to identify individuals and to associate a biological sample with an individual. Determination of which nucleotides occupy a set of SNP positions in an individual identifies a set of SNP markers that distinguishes the individual. The more SNP positions that are analyzed, the lower the probability that the set of SNPs in one individual is the same as that in an unrelated individual. Preferably, if multiple sites are analyzed, the sites are unlinked (i.e., inherited independently). Thus, preferred sets of SNPs can be selected from among the SNPs disclosed herein, which may include SNPs on different chromosomes, SNPs on different chromosome arms, and/or SNPs that are dispersed over substantial distances along the same chromosome arm.

[0229] Furthermore, among the SNPs disclosed herein, preferred SNPs for use in certain forensic/human identification applications include SNPs located at degenerate codon positions (i.e., the third position in certain codons which can be one of two or more alternative nucleotides and still encode the same amino acid), since these SNPs do not affect the encoded protein. SNPs that do not affect the encoded protein are expected to be under less selective pressure and are therefore expected to be more polymorphic in a population, which is typically an advantage for forensic/human identification applications. However, for certain forensics/human identification applications, such as predicting phenotypic characteristics (e.g., inferring ancestry or inferring one or more physical characteristics of an individual) from a DNA sample, it may be desirable to utilize SNPs that affect the encoded protein.

[0230] For the SNP disclosed in Tables 1-2 (which are identified as "Applera" SNP source), Tables 1-2 provide SNP allele frequencies obtained by re-sequencing the DNA of chromosomes from 39 individuals. The allele frequencies provided in Tables 1-2 enable the SNP to be readily used for human identification applications. The closer that the frequency of the minor allele at a particular SNP site is to 50%, the greater the ability of that SNP to discriminate between different individuals in a population since it becomes increasingly likely that two randomly selected individuals would have different alleles at that SNP site. Using the SNP allele frequency provided in Tables 1-2, one of ordinary skill in the art could readily select a subset of SNPs for which the frequency of the minor allele is, for example, at least 1%, 2%, 5%, 10%, 20%, 25%, 30%, 40%, 45%, or 50%, or any other frequency in-between. Thus, since Tables 1-2 provide allele frequency based on the re-sequencing of the chromosomes from 39 individuals, a subset of SNPs could readily be selected for human identification in which the total allele count of the minor allele at a particular SNP site is, for example, at least 1, 2, 4, 8, 10, 16, 20, 24, 30, 32, 36, 38, 39, 40, or any other number in-between.

[0231] Furthermore, Tables 1-2 also provide population group (interchangeably referred to herein as ethnic or racial groups) information coupled with the extensive allele frequency information. For example, the group of 39 individuals whose DNA was re-sequenced was made-up of 20 Caucasians and 19 African-Americans. This population group information enables further refinement of SNP selection for human identification. For example, preferred SNPs for human identification can be selected that have similar allele frequencies in both the Caucasian and African-American populations; thus, for example, SNPs can be selected that have equally high discriminatory power in both populations. Alternatively, SNPs can be selected for which there is a statistically significant difference in allele frequencies between the Caucasian and African-American populations (as an extreme example, a particular allele may be observed only in either the Caucasian or the African-American population group but not observed in the other population group); such SNPs are useful, for example, for predicting the race/ethnicity of an unknown perpetrator from a biological sample such as a hair or blood stain recovered at a crime scene. For a discussion of using SNPs to predict ancestry from a DNA sample, including statistical methods, see Frudakis et al., "A Classifier for the SNP-Based Inference of Ancestry", Journal of Forensic Sciences 2003; 48(4):771-782.

[0232] SNPs have numerous advantages over other types of polymorphic markers, such as short tandem repeats (STRs). For example, SNPs can be easily scored and are amenable to automation, making SNPs the markers of choice for large-scale forensic databases. SNPs are found in much greater abundance throughout the genome than repeat polymorphisms. Population frequencies of two polymorphic forms can usually be determined with greater accuracy than those of multiple polymorphic forms at multi-allelic loci. SNPs are mutationaly more stable than repeat polymorphisms.

SNPs are not susceptible to artefacts such as stutter bands that can hinder analysis. Stutter bands are frequently encountered when analyzing repeat polymorphisms, and are particularly troublesome when analyzing samples such as crime scene samples that may contain mixtures of DNA from multiple sources. Another significant advantage of SNP markers over STR markers is the much shorter length of nucleic acid needed to score a SNP. For example, STR markers are generally several hundred base pairs in length. A SNP, on the other hand, comprises a single nucleotide, and generally a short conserved region on either side of the SNP position for primer and/or probe binding. This makes SNPs more amenable to typing in highly degraded or aged biological samples that are frequently encountered in forensic casework in which DNA may be fragmented into short pieces.

[0233] SNPs also are not subject to microvariant and "off-ladder" alleles frequently encountered when analyzing STR loci. Microvariants are deletions or insertions within a repeat unit that change the size of the amplified DNA product so that the amplified product does not migrate at the same rate as reference alleles with normal sized repeat units. When separated by size, such as by electrophoresis on a polyacrylamide gel, microvariants do not align with a reference allelic ladder of standard sized repeat units, but rather migrate between the reference alleles. The reference allelic ladder is used for precise sizing of alleles for allele classification; therefore alleles that do not align with the reference allelic ladder lead to substantial analysis problems. Furthermore, when analyzing multi-allelic repeat polymorphisms, occasionally an allele is found that consists of more or less repeat units than has been previously seen in the population, or more or less repeat alleles than are included in a reference allelic ladder. These alleles will migrate outside the size range of known alleles in a reference allelic ladder, and therefore are referred to as "off-ladder" alleles. In extreme cases, the allele may contain so few or so many repeats that it migrates well out of the range of the reference allelic ladder. In this situation, the allele may not even be observed, or, with multiplex analysis, it may migrate within or close to the size range for another locus, further confounding analysis.

[0234] SNP analysis avoids the problems of microvariants and off-ladder alleles encountered in STR analysis. Importantly, microvariants and off-ladder alleles may provide significant problems, and may be completely missed, when using analysis methods such as oligonucleotide hybridization arrays, which utilize oligonucleotide probes specific for certain known alleles. Furthermore, off-ladder alleles and microvariants encountered with STR analysis, even when correctly typed, may lead to improper statistical analysis, since their frequencies in the population are generally unknown or poorly characterized, and therefore the statistical significance of a matching genotype may be questionable. All these advantages of SNP analysis are considerable in light of the consequences of most DNA identification cases, which may lead to life imprisonment for an individual, or re-association of remains to the family of a deceased individual.

[0235] DNA can be isolated from biological samples such as blood, bone, hair, saliva, or semen, and compared with the DNA from a reference source at particular SNP positions. Multiple SNP markers can be assayed simultaneously in order to increase the power of discrimination and the statistical significance of a matching genotype. For example, oligonucleotide arrays can be used to genotype a large number of SNPs simultaneously. The SNPs described herein can be assayed in combination with other polymorphic genetic markers, such as other SNPs known in the art or STRs, in order to identify an individual or to associate an individual with a particular biological sample.

[0236] Furthermore, the SNPs described herein can be genotyped for inclusion in a database of DNA genotypes, for example, a criminal DNA databank such as the FBI's Combined DNA Index System (CODIS) database. A genotype obtained from a biological sample of unknown source can then be queried against the database to find a matching genotype, with the SNPs described herein providing nucleotide positions at which to compare the known and unknown DNA sequences for identity. Accordingly, described herein is a database comprising novel SNPs or SNP alleles described herein (e.g., the database can comprise information indicating which alleles are possessed by individual members of a population at one or more novel SNP sites described herein), such as for use in forensics, biometrics, or other human identification applications. Such a database typically comprises a computer-based system in which the SNPs or SNP alleles described herein are recorded on a computer readable medium (see the section of the present specification entitled "Computer-Related Embodiments").

[0237] The SNPs described herein can also be assayed for use in paternity testing. The object of paternity testing is usually to determine whether a male is the father of a child. In most cases, the mother of the child is known and thus, the mother's contribution to the child's genotype can be traced. Paternity testing investigates whether the part of the child's genotype not attributable to the mother is consistent with that of the putative father. Paternity testing can be performed by analyzing sets of polymorphisms in the putative father and the child, with the SNPs described herein providing nucleotide positions at which to compare the putative father's and child's DNA sequences for identity. If the set of polymorphisms in the child attributable to the father does not match the set of polymorphisms of the putative father, it can be concluded, barring experimental error, that the putative father is not the father of the child. If the set of polymorphisms in the child attributable to the father match the set of polymorphisms of the putative father, a statistical calculation can be performed to determine the probability of coincidental match, and a conclusion drawn as to the likelihood that the putative father is the true biological father of the child.

[0238] In addition to paternity testing, SNPs are also useful for other types of kinship testing, such as for verifying familial relationships for immigration purposes, or for cases in which an individual alleges to be related to a deceased

individual in order to claim an inheritance from the deceased individual, etc. For further information regarding the utility of SNPs for paternity testing and other types of kinship testing, including methods for statistical analysis, see Krawczak, "Informativity assessment for biallelic single nucleotide polymorphisms", Electrophoresis 1999 Jun;20(8):1676-81.

[0239] The use of the SNPs described herein for human identification further extends to various authentication systems, commonly referred to as biometric systems, which typically convert physical characteristics of humans (or other organisms) into digital data. Biometric systems include various technological devices that measure such unique anatomical or physiological characteristics as finger, thumb, or palm prints; hand geometry; vein patterning on the back of the hand; blood vessel patterning of the retina and color and texture of the iris; facial characteristics; voice patterns; signature and typing dynamics; and DNA. Such physiological measurements can be used to verify identity and, for example, restrict or allow access based on the identification. Examples of applications for biometrics include physical area security, computer and network security, aircraft passenger check-in and boarding, financial transactions, medical records access, government benefit distribution, voting, law enforcement, passports, visas and immigration, prisons, various military applications, and for restricting access to expensive or dangerous items, such as automobiles or guns (see, for example, O'Connor, *Stanford Technology Law Review* and U.S. Patent No. 6,119,096).

[0240] Groups of SNPs, particularly the SNPs described herein, can be typed to uniquely identify an individual for biometric applications such as those described above. Such SNP typing can readily be accomplished using, for example, DNA chips/arrays. Preferably, a minimally invasive means for obtaining a DNA sample is utilized. For example, PCR amplification enables sufficient quantities of DNA for analysis to be obtained from buccal swabs or fingerprints, which contain DNA-containing skin cells and oils that are naturally transferred during contact.

[0241] Further information regarding techniques for using SNPs in forensic/human identification applications can be found in, for example, Current Protocols in Human Genetics, John Wiley & Sons, N.Y. (2002),14.1-14.7.

VARIANT PROTEINS, ANTIBODIES, VECTORS & HOST CELLS, & USES THEREOF

Variant Proteins Encoded by SNP-Containing Nucleic Acid Molecules

[0242] Described herein are SNP-containing nucleic acid molecules, many of which encode proteins having variant amino acid sequences as compared to the art-known (i.e., wild-type) proteins. Amino acid sequences encoded by the polymorphic nucleic acid molecules described herein is provided as SEQ ID NO:2 in Table 1 and the Sequence Listing. These variants will generally be referred to herein as variant proteins/peptides/polypeptides, or polymorphic proteins/peptides/polypeptides of the present invention. The terms "protein", "peptide", and "polypeptide" are used herein interchangeably.

[0243] A variant protein described herein may be encoded by, for example, a nonsynonymous nucleotide substitution at any one of the cSNP positions disclosed herein. In addition, variant proteins may also include proteins whose expression, structure, and/or function is altered by a SNP disclosed herein, such as a SNP that creates or destroys a stop codon, a SNP that affects splicing, and a SNP in control/regulatory elements, e.g. promoters, enhancers, or transcription factor binding domains.

[0244] As used herein, a protein or peptide is said to be "isolated" or "purified" when it is substantially free of cellular material or chemical precursors or other chemicals. The variant proteins described herein can be purified to homogeneity or other lower degrees of purity. The level of purification will be based on the intended use. The key feature is that the preparation allows for the desired function of the variant protein, even if in the presence of considerable amounts of other components.

[0245] As used herein, "substantially free of cellular material" includes preparations of the variant protein having less than about 30% (by dry weight) other proteins (i.e., contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins. When the variant protein is recombinantly produced, it can also be substantially free of culture medium, i.e., culture medium represents less than about 20% of the volume of the protein preparation.

[0246] The language "substantially free of chemical precursors or other chemicals" includes preparations of the variant protein in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the variant protein having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

[0247] An isolated variant protein may be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant host cells), or synthesized using known protein synthesis methods. For example, a nucleic acid molecule containing SNP(s) encoding the variant protein can be cloned into an expression vector, the expression vector introduced into a host cell, and the variant protein expressed in the host cell. The variant protein can then be isolated from the cells by any appropriate purification scheme using standard protein purification techniques.

Examples of these techniques are described in detail below (Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

[0248] Described herein are isolated variant proteins that comprise, consist of or consist essentially of amino acid sequences that contain one or more variant amino acids encoded by one or more codons which contain a SNP described herein.

[0249] Accordingly, described herein are variant proteins that consist of amino acid sequences that contain one or more amino acid polymorphisms (or truncations or extensions due to creation or destruction of a stop codon, respectively) encoded by the SNP provided in Table 1 and/or Table 2. A protein consists of an amino acid sequence when the amino acid sequence is the entire amino acid sequence of the protein.

[0250] Described herein are variant proteins that consist essentially of amino acid sequences that contain one or more amino acid polymorphisms (or truncations or extensions due to creation or destruction of a stop codon, respectively) encoded by the SNP provided in Table 1 and/or Table 2. A protein consists essentially of an amino acid sequence when such an amino acid sequence is present with only a few additional amino acid residues in the final protein.

[0251] Further, described herein are variant proteins that comprise amino acid sequences that contain one or more amino acid polymorphisms (or truncations or extensions due to creation or destruction of a stop codon, respectively) encoded by the SNP provided in Table 1 and/or Table 2. A protein comprises an amino acid sequence when the amino acid sequence is at least part of the final amino acid sequence of the protein. In such a fashion, the protein may contain only the variant amino acid sequence or have additional amino acid residues, such as a contiguous encoded sequence that is naturally associated with it or heterologous amino acid residues. Such a protein can have a few additional amino acid residues or can comprise many more additional amino acids. A brief description of how various types of these proteins can be made and isolated is provided below.

[0252] The variant proteins described herein can be attached to heterologous sequences to form chimeric or fusion proteins. Such chimeric and fusion proteins comprise a variant protein operatively linked to a heterologous protein having an amino acid sequence not substantially homologous to the variant protein. "Operatively linked" indicates that the coding sequences for the variant protein and the heterologous protein are ligated in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the variant protein. In another embodiment, the fusion protein is encoded by a fusion polynucleotide that is synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see Ausubel et al., Current Protocols in Molecular Biology, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST protein). A variant protein-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the variant protein.

[0253] In many uses, the fusion protein does not affect the activity of the variant protein. The fusion protein can include, but is not limited to, enzymatic fusion proteins, for example, beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, MYC-tagged, HI-tagged and Ig fusions. Such fusion proteins, particularly poly-His fusions, can facilitate their purification following recombinant expression. In certain host cells (e.g., mammalian host cells), expression and/or secretion of a protein can be increased by using a heterologous signal sequence. Fusion proteins are further described in, for example, Terpe, "Overview of tag protein fusions: from molecular and biochemical fundamentals to commercial systems", Appl Microbiol Biotechnol: 2003 Jan;60(5):523-33. Epub 2002 Nov 07; Graddis et al., "Designing proteins that work using recombinant technologies", Curr Pharm Biotechnol. 2002 Dec;3(4):285-97; and Nilsson et al., "Affinity fusion strategies for detection, purification, and immobilization of recombinant proteins", Protein Expr Purif. 1997 Oct;11(1):1-16.

[0254] The present disclosure also relates to further obvious variants of the variant polypeptides described herein, such as naturally-occurring mature forms (e.g., alleleic variants), non-naturally occurring recombinantly-derived variants, and orthologs and paralogs of such proteins that share sequence homology. Such variants can readily be generated using art-known techniques in the fields of recombinant nucleic acid technology and protein biochemistry. It is understood, however, that variants exclude those known in the prior art before the present disclosure.

[0255] Further variants of the variant polypeptides disclosed in Table 1 can comprise an amino acid sequence that shares at least 70-80%, 80-85%, 85-90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with an amino acid sequence disclosed in Table 1 (or a fragment thereof) and that includes a novel amino acid residue (allele) disclosed in Table 1 (which is encoded by a novel SNP allele). Thus, described herein are polypeptides that have a certain degree of sequence variation compared with the polypeptide sequences shown in Table 1, but that contain a novel amino acid residue (allele) encoded by a novel SNP allele disclosed herein. In other words, as long as a polypeptide contains a novel amino acid residue disclosed herein, other portions of the polypeptide that flank the novel amino acid residue can vary to some degree from the polypeptide sequences shown in Table 1.

[0256] Full-length pre-processed forms, as well as mature processed forms, of proteins that comprise one of the amino acid sequences disclosed herein can readily be identified as having complete sequence identity to one of the variant proteins described herein as well as being encoded by the same genetic locus as the variant proteins provided herein.

[0257] Orthologs of a variant peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of a variant peptide as well as being encoded by a gene from another organism. Preferred orthologs will be isolated from non-human mammals, preferably primates, for the development of human therapeutic targets and agents. Such orthologs can be encoded by a nucleic acid sequence that hybridizes to a variant peptide-encoding nucleic acid molecule under moderate to stringent conditions depending on the degree of relatedness of the two organisms yielding the homologous proteins.

[0258] Variant proteins include, but are not limited to, proteins containing deletions, additions and substitutions in the amino acid sequence caused by the SNPs described herein. One class of substitutions is conserved amino acid substitutions in which a given amino acid in a polypeptide is substituted for another amino acid of like characteristics. Typical conservative substitutions are replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu; substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in, for example, Bowie et al., Science 247:1306-1310 (1990).

[0259] Variant proteins can be fully functional or can lack function in one or more activities, e.g. ability to bind another molecule, ability to catalyze a substrate, ability to mediate signaling, etc. Fully functional variants typically contain only conservative variations or variations in non-critical residues or in non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, truncations or extensions, or a substitution, insertion, inversion, or deletion of a critical residue or in a critical region.

[0260] Amino acids that are essential for function of a protein can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham et al., Science 244:1081-1085 (1989)), particularly using the amino acid sequence and polymorphism information provided in Table 1. The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as enzyme activity or in assays such as an *in vitro* proliferative activity. Sites that are critical for binding partner/substrate binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., J. Mol. Biol. 224:899-904 (1992); de Vos et al. Science 255:306-312 (1992)).

[0261] Polypeptides can contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally occurring amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other post-translational modifications, or by chemical modification techniques well known in the art. Accordingly, the variant proteins described herein also encompass derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code, in which a substituent group is included, in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (e.g., polyethylene glycol), or in which additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence for purification of the mature polypeptide or a pro-protein sequence.

[0262] Known protein modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

[0263] Such protein modifications are well known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as Proteins - Structure and Molecular Properties, 2nd Ed., T.E. Creighton, W. H. Freeman and Company, New York (1993); Wold, F., Posttranslational Covalent Modification of Proteins, B.C. Johnson, Ed., Academic Press, New York 1-12 (1983); Seifter et al., Meth. Enzymol. 182: 626-646 (1990); and Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992).

[0264] For reference only, described herein are fragments of the variant proteins in which the fragments contain one or more amino acid sequence variations (e.g., substitutions, or truncations or extensions due to creation or destruction of a stop codon) encoded by one or more SNPs disclosed herein. The fragments described herein, however, are not to be construed as encompassing fragments that have been disclosed in the prior art before the present disclosure.

[0265] As used herein, a fragment may comprise at least about 4, 8,10, 12, 14, 16, 18, 20, 25, 30, 50, 100 (or any other number in-between) or more contiguous amino acid residues from a variant protein, wherein at least one amino acid residue is affected by a SNP described herein, e.g., a variant amino acid residue encoded by a nonsynonymous

nucleotide substitution at a cSNP position described herein. The variant amino acid encoded by a cSNP may occupy any residue position along the sequence of the fragment. Such fragments can be chosen based on the ability to retain one or more of the biological activities of the variant protein or the ability to perform a function, e.g., act as an immunogen. Particularly important fragments are biologically active fragments. Such fragments will typically comprise a domain or motif of a variant protein described herein, e.g., active site, transmembrane domain, or ligand/substrate binding domain. Other fragments include, but are not limited to, domain or motif-containing fragments, soluble peptide fragments, and fragments containing immunogenic structures. Predicted domains and functional sites are readily identifiable by computer programs well known to those of skill in the art (e.g., PROSITE analysis) (Current Protocols in Protein Science, John Wiley & Sons, N.Y. (2002)).

Uses of Variant Proteins

[0266] The variant proteins described herein can be used in a variety of ways, including but not limited to, in assays to determine the biological activity of a variant protein, such as in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another type of immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the variant protein (or its binding partner) in biological fluids; as a marker for cells or tissues in which it is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); as a target for screening for a therapeutic agent; and as a direct therapeutic agent to be administered into a human subject. Any of the variant proteins disclosed herein may be developed into reagent grade or kit format for commercialization as research products. Methods for performing the uses listed above are well known to those skilled in the art (see, e.g., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Sambrook and Russell, 2000, and Methods in Enzymology: Guide to Molecular Cloning Techniques, Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987).

[0267] In a specific embodiment of the invention, the methods of the present invention include detection of one or more variant proteins disclosed herein. Variant proteins are disclosed in Table 1 and in the Sequence Listing as SEQ ID NO:2. Detection of such proteins can be accomplished using, for example, antibodies, small molecule compounds, aptamers, ligands/substrates, other proteins or protein fragments, or other protein-binding agents. Preferably, protein detection agents are specific for a variant protein described herein and can therefore discriminate between a variant protein described herein and the wild-type protein or another variant form. This can generally be accomplished by, for example, selecting or designing detection agents that bind to the region of a protein that differs between the variant and wild-type protein, such as a region of a protein that contains one or more amino acid substitutions that is/are encoded by a non-synonymous cSNP described herein, or a region of a protein that follows a nonsense mutation-type SNP that creates a stop codon thereby leading to a shorter polypeptide, or a region of a protein that follows a read-through mutation-type SNP that destroys a stop codon thereby leading to a longer polypeptide in which a portion of the polypeptide is present in one version of the polypeptide but not the other.

[0268] In another specific aspect, the variant proteins described herein are used as targets for diagnosing myocardial infarction or for determining predisposition to myocardial infarction in a human. Accordingly, the invention provides methods for detecting the presence of, or levels of, one or more variant proteins of the present invention in a cell, tissue, or organism. Such methods typically involve contacting a test sample with an agent (e.g., an antibody, small molecule compound, or peptide) capable of interacting with the variant protein such that specific binding of the agent to the variant protein can be detected. Such an assay can be provided in a single detection format or a multi-detection format such as an array, for example, an antibody or aptamer array (arrays for protein detection may also be referred to as "protein chips"). The variant protein of interest can be isolated from a test sample and assayed for the presence of a variant amino acid sequence encoded by one or more SNPs described herein. The SNPs may cause changes to the protein and the corresponding protein function/activity, such as through non-synonymous substitutions in protein coding regions that can lead to amino acid substitutions, deletions, insertions, and/or rearrangements; formation or destruction of stop codons; or alteration of control elements such as promoters. SNPs may also cause inappropriate post-translational modifications.

[0269] One preferred agent for detecting a variant protein in a sample is an antibody capable of selectively binding to a variant form of the protein (antibodies are described in greater detail in the next section). Such samples include, for example, tissues, cells, and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

[0270] *In vitro* methods for detection of the variant proteins associated with myocardial infarction that are disclosed herein and fragments thereof include, but are not limited to, enzyme linked immunosorbent assays (ELISAs), radioimmunoassays (RIA), Western blots, immunoprecipitations, immunofluorescence, and protein arrays/chips (e.g., arrays of antibodies or aptamers). For further information regarding immunoassays and related protein detection methods, see Current Protocols in Immunology, John Wiley & Sons, N.Y., and Hage, "Immunoassays", Anal Chem. 1999 Jun 15;71 (12):294R-304R.

[0271] Additional analytic methods of detecting amino acid variants include, but are not limited to, altered electrophoretic mobility, altered tryptic peptide digest, altered protein activity in cell-based or cell-free assay, alteration in ligand or antibody-binding pattern, altered isoelectric point, and direct amino acid sequencing.

[0272] Alternatively, variant proteins can be detected *in vivo* in a subject by introducing into the subject a labeled antibody (or other type of detection reagent) specific for a variant protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[0273] Other uses of the variant peptides described herein are based on the class or action of the protein: For example, proteins isolated from humans and their mammalian orthologs serve as targets for identifying agents (e.g., small molecule drugs or antibodies) for use in therapeutic applications, particularly for modulating a biological or pathological response in a cell or tissue that expresses the protein. Pharmaceutical agents can be developed that modulate protein activity.

[0274] As an alternative to modulating gene expression, therapeutic compounds can be developed that modulate protein function. For example, many SNPs disclosed herein affect the amino acid sequence of the encoded protein (e.g., non-synonymous cSNPs and nonsense mutation-type SNPs). Such alterations in the encoded amino acid sequence may affect protein function, particularly if such amino acid sequence variations occur in functional protein domains, such as catalytic domains, ATP-binding domains, or ligand/substrate binding domains. It is well established in the art that variant proteins having amino acid sequence variations in functional domains can cause or influence pathological conditions. In such instances, compounds (e.g., small molecule drugs or antibodies) can be developed that target the variant protein and modulate (e.g., up- or down-regulate) protein function/activity.

[0275] The therapeutic methods described herein further include methods that target one or more variant proteins described herein Variant proteins can be targeted using, for example, small molecule compounds, antibodies, aptamers, ligands/substrates, other proteins, or other protein-binding agents. Additionally, the skilled artisan will recognize that the novel protein variants (and polymorphic nucleic acid molecules) disclosed in Table 1 may themselves be directly used as therapeutic agents by acting as competitive inhibitors of corresponding art-known proteins (or nucleic acid molecules such as mRNA molecules).

[0276] The variant proteins described herein are particularly useful in drug screening assays, in cell-based or cell-free systems. Cell-based systems can utilize cells that naturally express the protein, a biopsy specimen, or cell cultures. In one embodiment, cell-based assays involve recombinant host cells expressing the variant protein. Cell-free assays can be used to detect the ability of a compound to directly bind to a variant protein or to the corresponding SNP-containing nucleic acid fragment that encodes the variant protein.

[0277] A variant protein described herein, as well as appropriate fragments thereof, can be used in high-throughput screening assays to test candidate compounds for the ability to bind and/or modulate the activity of the variant protein. These candidate compounds can be further screened against a protein having normal function (e.g., a wild-type/non-variant protein) to further determine the effect of the compound on the protein activity. Furthermore, these compounds can be tested in animal or invertebrate systems to determine *in vivo* activity/effectiveness. Compounds can be identified that activate (agonists) or inactivate (antagonists) the variant protein, and different compounds can be identified that cause various degrees of activation or inactivation of the variant protein.

[0278] Further, the variant proteins can be used to screen a compound for the ability to stimulate or inhibit interaction between the variant protein and a target molecule that normally interacts with the protein. The target can be a ligand, a substrate or a binding partner that the protein normally interacts with (for example, epinephrine or norepinephrine). Such assays typically include the steps of combining the variant protein with a candidate compound under conditions that allow the variant protein, or fragment thereof, to interact with the target molecule, and to detect the formation of a complex between the protein and the target or to detect the biochemical consequence of the interaction with the variant protein and the target, such as any of the associated effects of signal transduction.

[0279] Candidate compounds include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, e.g., Lam et al., Nature 354:82-84 (1991); Houghten et al., Nature 354:84-86 (1991)) and combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; 2) phosphopeptides (e.g., members of random and partially degenerate, directed phosphopeptide libraries, see, e.g., Songyang et al., Cell 72:767-778 (1993)); 3) antibodies (e.g., polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, $F(ab)_2$, Fab expression library fragments, and epitope-binding fragments of antibodies); and 4) small organic and inorganic molecules (e.g., molecules obtained from combinatorial and natural product libraries).

[0280] One candidate compound is a soluble fragment of the variant protein that competes for ligand binding. Other candidate compounds include mutant proteins or appropriate fragments containing mutations that affect variant protein function and thus compete for ligand. Accordingly, a fragment that competes for ligand, for example with a higher affinity, or a fragment that binds ligand but does not allow release, is described herein.

[0281] For reference only, the description further includes other end point assays to identify compounds that modulate (stimulate or inhibit) variant protein activity. The assays typically involve an assay of events in the signal transduction pathway that indicate protein activity. Thus, the expression of genes that are up or down-regulated in response to the

variant protein dependent signal cascade can be assayed. In one embodiment, the regulatory region of such genes can be operably linked to a marker that is easily detectable, such as luciferase. Alternatively, phosphorylation of the variant protein, or a variant protein target, could also be measured. Any of the biological or biochemical functions mediated by the variant protein can be used as an endpoint assay. These include all of the biochemical or biological events described herein, in the references cited herein, for these endpoint assay targets, and other functions known to those of ordinary skill in the art.

[0282] Binding and/or activating compounds can also be screened by using chimeric variant proteins in which an amino terminal extracellular domain or parts thereof, an entire transmembrane domain or subregions, and/or the carboxyl terminal intracellular domain or parts thereof, can be replaced by heterologous domains or subregions. For example, a substrate-binding region can be used that interacts with a different substrate than that which is normally recognized by a variant protein. Accordingly, a different set of signal transduction components is available as an end-point assay for activation. This allows for assays to be performed in other than the specific host cell from which the variant protein is derived.

[0283] The variant proteins are also useful in competition binding assays in methods designed to discover compounds that interact with the variant protein. Thus, a compound can be exposed to a variant protein under conditions that allow the compound to bind or to otherwise interact with the variant protein. A binding partner, such as ligand, that normally interacts with the variant protein is also added to the mixture. If the test compound interacts with the variant protein or its binding partner, it decreases the amount of complex formed or activity from the variant protein. This type of assay is particularly useful in screening for compounds that interact with specific regions of the variant protein (Hodgson, Bio/technology, 1992, Sept 10(9), 973-80).

[0284] To perform cell-free drug screening assays, it is sometimes desirable to immobilize either the variant protein or a fragment thereof, or its target molecule, to facilitate separation of complexes from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Any method for immobilizing proteins on matrices can be used in drug screening assays. In one embodiment, a fusion protein containing an added domain allows the protein to be bound to a matrix. For example, glutathione-S-transferase/^{125}I fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the cell lysates (e.g., ^{35}S-labeled) and a candidate compound, such as a drug candidate, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads can be washed to remove any unbound label, and the matrix immobilized and radiolabel determined directly, or in the supernatant after the complexes are dissociated. Alternatively, the complexes can be dissociated from the matrix, separated by SDS-PAGE, and the level of bound material found in the bead fraction quantitated from the gel using standard electrophoretic techniques.

[0285] Either the variant protein or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Alternatively, antibodies reactive with the variant protein but which do not interfere with binding of the variant protein to its target molecule can be derivatized to the wells of the plate, and the variant protein trapped in the wells by antibody conjugation. Preparations of the target molecule and a candidate compound are incubated in the variant protein-presenting wells and the amount of complex trapped in the well can be quantitated. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the protein target molecule, or which are reactive with variant protein and compete with the target molecule, and enzyme-linked assays that rely on detecting an enzymatic activity associated with the target molecule.

[0286] Modulators of variant protein activity identified according to these drug screening assays can be used to treat a subject with a disorder mediated by the protein pathway, such as myocardial infarction. These methods of treatment typically include the steps of administering the modulators of protein activity in a pharmaceutical composition to a subject in need of such treatment.

[0287] The variant proteins, or fragments thereof, disclosed herein can themselves be directly used to treat a disorder characterized by an absence of, inappropriate, or unwanted expression or activity of the variant protein. Accordingly, methods for treatment include the use of a variant protein disclosed herein or fragments thereof.

[0288] For reference only, variant proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos et al. (1993) Cell 72:223-232; Madura et al. (1993) J. Biol. Chem. 268: 12046-12054; Bartel et al. (1993) Biotechniques 14:920-924; Iwabuchi et al. (1993) Oncogene 8:1693-1696; and Brent WO94/10300) to identify other proteins that bind to or interact with the variant protein and are involved in variant protein activity. Such variant protein-binding proteins are also likely to be involved in the propagation of signals by the variant proteins or variant protein targets as, for example, elements of a protein-mediated signaling pathway. Alternatively, such variant protein-binding proteins are inhibitors of the variant protein.

[0289] The two-hybrid system is based on the modular nature of most transcription factors, which typically consist of separable DNA-binding and activation domains. Briefly, the assay typically utilizes two different DNA constructs. In one construct, the gene that codes for a variant protein is fused to a gene encoding the DNA binding domain of a known

transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation.domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a variant protein-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected, and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein that interacts with the variant protein.

Antibodies Directed to Variant Proteins

[0290] For reference only, described herein are antibodies that selectively bind to the variant proteins disclosed herein and fragments thereof. Such antibodies may be used to quantitatively or qualitatively detect the variant proteins described herein. As used herein, an antibody selectively binds a target variant protein when it binds the variant protein and does not significantly bind to non-variant proteins, i.e., the antibody does not significantly bind to normal, wild-type, or art-known proteins that do not contain a variant amino acid sequence due to one or more SNPs described herein (variant amino acid sequences may be due to, for example, nonsynonymous cSNPs, nonsense SNPs that create a stop codon, thereby causing a truncation of a polypeptide or SNPs that cause read-through mutations resulting in an extension of a polypeptide).

[0291] As used herein, an antibody is defined in terms consistent with that recognized in the art: they are multi-subunit proteins produced by an organism in response to an antigen challenge. The antibodies described herein include both monoclonal antibodies and polyclonal antibodies, as well as antigen-reactive proteolytic fragments of such antibodies, such as Fab, $F(ab)'_2$, and Fv fragments. In addition, an antibody described herein further includes any of a variety of engineered antigen-binding molecules such as a chimeric antibody (U.S. Patent Nos. 4,816,567 and 4,816,397; Morrison et al., Proc. Natl. Acad Sci. USA, 81:6851, 1984; Neuberger et al., Nature 312:604, 1984), a humanized antibody (U.S. Patent Nos. 5,693,762; 5,585,089; and 5,565,332), a single-chain Fv (U.S. Patent No. 4,946,778; Ward et al., Nature 334:544, 1989), a bispecific antibody with two binding specificities (Segal et al., J. Immunol. Methods 248:1, 2001; Carter, J. Immunol. Methods 248:7, 2001), a diabody, a triabody, and a tetrabody (Todorovska et al., J. Immunol. Methods, 248: 47, 2001), as well as a Fab conjugate (dimer or trimer), and a minibody.

[0292] Many methods are known in the art for generating and/or identifying antibodies to a given target antigen (Harlow, Antibodies, Cold Spring Harbor Press, (1989)). In general, an isolated peptide (e.g., a variant protein described herein) is used as an immunogen and is administered to a mammalian organism, such as a rat, rabbit, hamster or mouse. Either a full-length protein, an antigenic peptide fragment (e.g., a peptide fragment containing a region that varies between a variant protein and a corresponding wild-type protein), or a fusion protein can be used. A protein used as an immunogen may be naturally-occurring, synthetic or recombinantly produced, and may be administered in combination with an adjuvant, including but not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substance such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol, and the like.

[0293] Monoclonal antibodies can be produced by hybridoma technology (Kohler and Milstein, Nature, 256:495, 1975), which immortalizes cells secreting a specific monoclonal antibody. The immortalized cell lines can be created *in vitro* by fusing two different cell types, typically lymphocytes, and tumor cells. The hybridoma cells may be cultivated *in vitro* or *in vivo.* Additionally, fully human antibodies can be generated by transgenic animals (He et al., J. Immunol., 169:595, 2002). Fd phage and Fd phagemid technologies may be used to generate and select recombinant antibodies *in vitro* (Hoogenboom and Chames, Immunol. Today 21:371, 2000; Liu et al., J. Mol. Biol. 315:1063, 2002). The complementarity-determining regions of an antibody can be identified, and synthetic peptides corresponding to such regions may be used to mediate antigen binding (U.S. Patent No. 5,637,677).

[0294] Antibodies are preferably prepared against regions or discrete fragments of a variant protein containing a variant amino acid sequence as compared to the corresponding wild-type protein (e.g., a region of a variant protein that includes an amino acid encoded by a nonsynonymous cSNP, a region affected by truncation caused by a nonsense SNP that creates a stop codon, or a region resulting from the destruction of a stop codon due to read-through mutation caused by a SNP). Furthermore, preferred regions will include those involved in function/activity and/or protein/binding partner interaction. Such fragments can be selected on a physical property, such as fragments corresponding to regions that are located on the surface of the protein, e.g., hydrophilic regions, or can be selected based on sequence uniqueness, or based on the position of the variant amino acid residue(s) encoded by the SNPs described herein. An antigenic fragment will typically comprise at least about 8-10 contiguous amino acid residues in which at least one of the amino acid residues is an amino acid affected by a SNP disclosed herein. The antigenic peptide can comprise, however, at least 12,14, 16, 20, 25, 50, 100 (or any other number in-between) or more amino acid residues, provided that at least one amino acid is affected by a SNP

[0295] Detection of an antibody described herein can be facilitated by coupling (i.e., physically linking) the antibody or an antigen-reactive fragment thereof to a detectable substance. Detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[0296] Antibodies, particularly the use of antibodies as therapeutic agents, are reviewed in: Morgan, "Antibody therapy for Alzheimer's disease", Expert Rev Vaccines. 2003 Feb;2(1):53-9; Ross et al., "Anticancer antibodies", Am J Clin Pathol. 2003 Apr;119(4):472-85; Goldenberg, "Advancing role of radiolabeled antibodies in the therapy of cancer", Cancer Immunol Immunother. 2003 May;52(5):281-96. Epub 2003 Mar 11; Ross et al., "Antibody-based therapeutics in oncology", Expert Rev Anticancer Ther. 2003 Feb;3(1):107-21; Cao et al., "Bispecific antibody conjugates in therapeutics". Adv Drug Deliv Rev. 2003 Feb 10;55(2):171-97; von Mehren et al., "Monoclonal antibody therapy for cancer", Annu Rev Med. 2003;54:343-69. Epub 2001 Dec 03; Hudson et al., "Engineered antibodies", Nat Med. 2003 Jan;9(1):129-34; Brekke et al., "Therapeutic antibodies for human diseases at the dawn of the twenty-first century", Nat Rev Drug Discov. 2003 Jan;2(1):52-62 (Erratum in: Nat Rev Drug Discov. 2003 Mar;2(3):240); Houdebine, "Antibody manufacture in transgenic animals and comparisons with other systems", Curr Opin Biotechnol. 2002 Dec;13(6):625-9; Andreakos et al., "Monoclonal antibodies in immune and inflammatory diseases", Curr Opin Biotechnol. 2002 Dec;13(6):615-20; Kellermann et al., "Antibody discovery: the use of transgenic mice to generate human monoclonal antibodies for therapeutics", Curr Opin Biotechnol. 2002 Dec;13(6):593-7; Pini et al., "Phage display and colony filter screening for high-throughput selection of antibody libraries", Comb Chem High Throughput Screen. 2002 Nov;5(7):503-10; Batra et al., "Pharmacokinetics and biodistribution of genetically engineered antibodies", Curr Opin Biotechnol. 2002 Dec;13(6):603-8; and Tangri et al., "Rationally engineered proteins or antibodies with absent or reduced immunogenicity", Curr Med Chem. 2002 Dec;9(24):2191-9.

Uses of Antibodies

[0297] For reference only, antibodies can be used to isolate the variant proteins described herein from a natural cell source or from recombinant host cells by standard techniques, such as affinity chromatography or immunoprecipitation. In addition, antibodies are useful for detecting the presence of a variant protein described herein in cells or tissues to determine the pattern of expression of the variant protein among various tissues in an organism and over the course of normal development or disease progression. Further, antibodies can be used to detect variant protein *in situ*, *in vitro,* in a bodily fluid, or in a cell lysate or supernatant in order to evaluate the amount and pattern of expression. Also, antibodies can be used to assess abnormal tissue distribution, abnormal expression during development, or expression in an abnormal condition, such as myocardial infarction. Additionally, antibody detection of circulating fragments of the full-length variant protein can be used to identify turnover.

[0298] Antibodies to the variant proteins described herein are also useful in pharmacogenomic analysis. Thus, antibodies against variant proteins encoded by alternative SNP alleles can be used to identify individuals that require modified treatment modalities.

[0299] Further, antibodies can be used to assess expression of the variant protein in disease states such as in active stages of the disease or in an individual with a predisposition to a disease related to the protein's function, particularly myocardial infarction. Antibodies specific for a variant protein encoded by a SNP-containing nucleic acid molecule described herein can be used to assay for the presence of the variant protein, such as to screen for predisposition to myocardial infarction as indicated by the presence of the variant protein.

[0300] Antibodies are also useful as diagnostic tools for evaluating the variant proteins in conjunction with analysis by electrophoretic mobility, isoelectric point, tryptic peptide digest, and other physical assays well known in the art.

[0301] Antibodies are also useful for tissue typing. Thus, where a specific variant protein has been correlated with expression in a specific tissue, antibodies that are specific for this protein can be used to identify a tissue type.

[0302] Antibodies can also be used to assess aberrant subcellular localization of a variant protein in cells in various tissues. The diagnostic uses can be applied, not only in genetic testing, but also in monitoring a treatment modality. Accordingly, where treatment is ultimately aimed at correcting the expression level or the presence of variant protein or aberrant tissue distribution or developmental expression of a variant protein, antibodies directed against the variant protein or relevant fragments can be used to monitor therapeutic efficacy.

[0303] The antibodies are also useful for inhibiting variant protein function, for example, by blocking the binding of a variant protein to a binding partner. These uses can also be applied in a therapeutic context in which treatment involves inhibiting a variant protein's function. An antibody can be used, for example, to block or competitively inhibit binding,

thus modulating (agonizing or antagonizing) the activity of a variant protein. Antibodies can be prepared against specific variant protein fragments containing sites required for function or against an intact variant protein that is associated with a cell or cell membrane. For *in vivo* administration, an antibody may be linked with an additional therapeutic payload such as a radionuclide, an enzyme, an immunogenic epitope, or a cytotoxic agent. Suitable cytotoxic agents include, but are not limited to, bacterial toxin such as diphtheria, and plant toxin such as ricin. The *in vivo* half-life of an antibody or a fragment thereof may be lengthened by pegylation through conjugation to polyethylene glycol (Leong et al., Cytokine 16:106, 2001).

[0304] Described herein are kits for using antibodies, such as kits for detecting the presence of a variant protein in a test sample. An exemplary kit can comprise antibodies such as a labeled or labelable antibody and a compound or agent for detecting variant proteins in a biological sample; means for determining the amount, or presence/absence of variant protein in the sample; means for comparing the amount of variant protein in the sample with a standard; and instructions for use.

Vectors and Host Cells

[0305] Also disclosed herein are vectors containing the SNP-containing nucleic acid molecules described herein. The term "vector" refers to a vehicle, preferably a nucleic acid molecule, which can transport a SNP-containing nucleic acid molecule. When the vector is a nucleic acid molecule; the SNP-containing nucleic acid molecule can be covalently linked to the vector nucleic acid. Such vectors include, but are not limited to, a plasmid, single or double stranded phage, a single or double stranded RNA or DNA viral vector, or artificial chromosome, such as a BAC, PAC, YAC, or MAC.

[0306] A vector can be maintained in a host cell as an extrachromosomal element where it replicates and produces additional copies of the SNP-containing nucleic acid molecules. Alternatively, the vector may integrate into the host cell genome and produce additional copies of the SNP-containing nucleic acid molecules when the host cell replicates.

[0307] Also disclosed herein are vectors for the maintenance (cloning vectors) or vectors for expression (expression vectors) of the SNP-containing nucleic acid molecules. The vectors can function in prokaryotic or eukaryotic cells or in both (shuttle vectors).

[0308] Expression vectors typically contain cis-acting regulatory regions that are operably linked in the vector to the SNP-containing nucleic acid molecules such that transcription of the SNP-containing nucleic acid molecules is allowed in a host cell. The SNP-containing nucleic acid molecules can also be introduced into the host cell with a separate nucleic acid molecule capable of affecting transcription. Thus, the second nucleic acid molecule may provide a trans-acting factor interacting with the cis-regulatory control region to allow transcription of the SNP-containing nucleic acid molecules from the vector. Alternatively, a trans-acting factor may be supplied by the host cell. Finally, a trans-acting factor can be produced from the vector itself. It is understood, however, that in some embodiments, transcription and/or translation of the nucleic acid molecules can occur in a cell-free system.

[0309] The regulatory sequences to which the SNP-containing nucleic acid molecules described herein can be operably linked include promoters for directing mRNA transcription. These include, but are not limited to, the left promoter from bacteriophage λ, the lac, TRP, and TAC promoters from *E. coli*, the early and late promoters from SV40, the CMV immediate early promoter, the adenovirus early and late promoters, and retrovirus long-terminal repeats.

[0310] In addition to control regions that promote transcription, expression vectors may also include regions that modulate transcription, such as repressor binding sites and enhancers. Examples include the SV40 enhancer, the cytomegalovirus immediate early enhancer, polyoma enhancer, adenovirus enhancers, and retrovirus LTR enhancers.

[0311] In addition to containing sites for transcription initiation and control, expression vectors can also contain sequences necessary for transcription termination and, in the transcribed region, a ribosome-binding site for translation. Other regulatory control elements for expression include initiation and termination codons as well as polyadenylation signals. A person of ordinary skill in the art would be aware of the numerous regulatory sequences that are useful in expression vectors (see, e.g., Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

[0312] A variety of expression vectors can be used to express a SNP-containing nucleic acid molecule. Such vectors include chromosomal, episomal, and virus-derived vectors, for example, vectors derived from bacterial plasmids, from bacteriophage, from yeast episomes, from yeast chromosomal elements, including yeast artificial chromosomes, from viruses such as baculoviruses, papovaviruses such as SV40, Vaccinia viruses, adenoviruses, poxviruses, pseudorabies viruses, and retroviruses. Vectors can also be derived from combinations of these sources such as those derived from plasmid and bacteriophage genetic elements, e.g., cosmids and phagemids. Appropriate cloning and expression vectors for prokaryotic and eukaryotic hosts are described in Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

[0313] The regulatory sequence in a vector may provide constitutive expression in one or more host cells (e.g., tissue specific expression) or may provide for inducible expression in one or more cell types such as by temperature, nutrient additive, or exogenous factor, e.g., a hormone or other ligand. A variety of vectors that provide constitutive or inducible

expression of a nucleic acid sequence in prokaryotic and eukaryotic host cells are well known to those of ordinary skill in the art.

[0314] A SNP-containing nucleic acid molecule can be inserted into the vector by methodology well-known in the art. Generally, the SNP-containing nucleic acid molecule that will ultimately be expressed is joined to an expression vector by cleaving the SNP-containing nucleic acid molecule and the expression vector with one or more restriction enzymes and then ligating the fragments together. Procedures for restriction enzyme digestion and ligation are well known to those of ordinary skill in the art.

[0315] The vector containing the appropriate nucleic acid molecule can be introduced into an appropriate host cell for propagation or expression using well-known techniques. Bacterial host cells include, but are not limited to, *E. coli, Streptomyces,* and *Salmonella typhimurium.* Eukaryotic host cells include, but are not limited to, yeast, insect cells such as *Drosophila,* animal cells such as COS and CHO cells, and plant cells.

[0316] As described herein, it may be desirable to express the variant peptide as a fusion protein. Accordingly, described herein are fusion vectors that allow for the production of the variant peptides. Fusion vectors can, for example, increase the expression of a recombinant protein, increase the solubility of the recombinant protein, and aid in the purification of the protein by acting, for example, as a ligand for affinity purification. A proteolytic cleavage site may be introduced at the junction of the fusion moiety so that the desired variant peptide can ultimately be separated from the fusion moiety. Proteolytic enzymes suitable for such use include, but are not limited to, factor Xa, thrombin, and enterokinase. Typical fusion expression vectors include pGEX (Smith et al., Gene 67:31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann et al., Gene 69:301-315 (1988)) and pET 11d (Studier et al., Gene Expression Technology: Methods in Enzymology 185:60-89 (1990)).

[0317] Recombinant protein expression can be maximized in a bacterial host by providing a genetic background wherein the host cell has an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, S., Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, California (1990) 119-128). Alternatively, the sequence of the SNP-containing nucleic acid molecule of interest can be altered to provide preferential codon usage for a specific host cell, for example, *E. coli* (Wada et al., Nucleic Acids Res. 20:2111-2118 (1992)).

[0318] The SNP-containing nucleic acid molecules can also be expressed by expression vectors that are operative in yeast. Examples of vectors for expression in yeast (e.g., S. *cerevisiae*) include pYepSec1 (Baldari, et al., EMBO J. 6:229-234 (1987)), pMFa (Kurjan et al., Cell 30:933-943(1982)), pJRY88 (Schultz et al., Gene 54:113-123 (1987)), and pYES2 (Invitrogen Corporation, San Diego, CA).

[0319] The SNP-containing nucleic acid molecules can also be expressed in insect cells using, for example, baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith et al., Mol. Cell Biol. 3:2156-2165 (1983)) and the pVL series (Lucklow et al., Virology 170: 31-39 (1989)).

[0320] In certain embodiments, the SNP-containing nucleic acid molecules described herein are expressed in mammalian cells using mammalian expression vectors. Examples of mammalian expression vectors include pCDM8 (Seed, B. Nature 329:840(1987)) and pMT2PC (Kaufman et al., EMBO J. 6:187-195 (1987)).

[0321] Described herein are vectors in which the SNP-containing nucleic acid molecules described herein are cloned into the vector in reverse orientation, but operably linked to a regulatory sequence that permits transcription of antisense RNA. Thus, an antisense transcript can be produced to the SNP-containing nucleic acid sequences described herein, including both coding and non-coding regions. Expression of this antisense RNA is subject to each of the parameters described above in relation to expression of the sense RNA (regulatory sequences, constitutive or inducible expression, tissue-specific expression).

[0322] For reference only, described herein are recombinant host cells containing the vectors described herein. Host cells therefore include, for example, prokaryotic cells, lower eukaryotic cells such as yeast, other eukaryotic cells such as insect cells, and higher eukaryotic cells such as mammalian cells.

[0323] The recombinant host cells can be prepared by introducing the vector constructs described herein into the cells by techniques readily available to persons of ordinary skill in the art. These include, but are not limited to, calcium phosphate transfection, DEAE-dextran-mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, lipofection, and other techniques such as those described in Sambrook and Russell, 2000, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

[0324] Host cells can contain more than one vector. Thus, different SNP-containing nucleotide sequences can be introduced in different vectors into the same cell. Similarly, the SNP-containing nucleic acid molecules can be introduced either alone or with other nucleic acid molecules that are not related to the SNP-containing nucleic acid molecules, such as those providing trans-acting factors for expression vectors. When more than one vector is introduced into a cell, the vectors can be introduced independently, co-introduced, or joined to the nucleic acid molecule vector.

[0325] In the case of bacteriophage and viral vectors, these can be introduced into cells as packaged or encapsulated virus by standard procedures for infection and transduction. Viral vectors can be replication-competent or replication-defective. In the case in which viral replication is defective, replication can occur in host cells that provide functions that complement the defects.

[0326] Vectors generally include selectable markers that enable the selection of the subpopulation of cells that contain the recombinant vector constructs. The marker can be inserted in the same vector that contains the SNP-containing nucleic acid molecules described herein or may be in a separate vector. Markers include, for example, tetracycline or ampicillin-resistance genes for prokaryotic host cells, and dihydrofolate reductase or neomycin resistance genes for eukaryotic host cells. However, any marker that provides selection for a phenotypic trait can be effective.

[0327] While the mature variant proteins can be produced in bacteria, yeast, mammalian cells, and other cells under the control of the appropriate regulatory sequences, cell-free transcription and translation systems can also be used to produce these variant proteins using RNA derived from the DNA constructs described herein.

[0328] Where secretion of the variant protein is desired, which is difficult to achieve with multi-transmembrane domain containing proteins such as G-protein-coupled receptors (GPCRs), appropriate secretion signals can be incorporated into the vector. The signal sequence can be endogenous to the peptides or heterologous to these peptides.

[0329] Where the variant protein is not secreted into the medium, the protein can be isolated from the host cell by standard disruption procedures, including freeze/thaw, sonication, mechanical disruption, use of lysing agents, and the like. The variant protein can then be recovered and purified by well-known purification methods including, for example, ammonium sulfate precipitation, acid extraction, anion or cationic exchange chromatography, phosphocellulose chromatography, hydrophobic-interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography, or high performance liquid chromatography.

[0330] It is also understood that, depending upon the host cell in which recombinant production of the variant proteins described herein occurs, they can have various glycosylation patterns, or may be non-glycosylated, as when produced in bacteria. In addition, the variant proteins may include an initial modified methionine in some cases as a result of a host-mediated process.

[0331] For further information regarding vectors and host cells, see Current Protocols in Molecular Biology, John Wiley & Sons, N.Y.

Uses of Vectors and Host Cells, and Transgenic Animals

[0332] Recombinant host cells that express the variant proteins described herein have a variety of uses. For example, the cells are useful for producing a variant protein that can be further purified into a preparation of desired amounts of the variant protein or fragments thereof. Thus, host cells containing expression vectors are useful for variant protein production.

[0333] Host cells are also useful for conducting cell-based assays involving the variant protein or variant protein fragments, such as those described above as well as other formats known in the art. Thus, a recombinant host cell expressing a variant protein is useful for assaying compounds that stimulate or inhibit variant protein function. Such an ability of a compound to modulate variant protein function may not be apparent from assays of the compound on the native/wild-type protein, or from cell-free assays of the compound. Recombinant host cells are also useful for assaying functional alterations in the variant proteins as compared with a known function.

[0334] Genetically-engineered host cells can be further used to produce non-human transgenic animals. A transgenic animal is preferably a non-human mammal, for example, a rodent, such as a rat or mouse, in which one or more of the cells of the animal include a transgene. A transgene is exogenous DNA containing a SNP described herein which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal in one or more of its cell types or tissues. Such animals are useful for studying the function of a variant protein *in vivo,* and identifying and evaluating modulators of variant protein activity. Other examples of transgenic animals include, but are not limited to, non-human primates, sheep, dogs, cows, goats, chickens, and amphibians. Transgenic non-human mammals such as cows and goats can be used to produce variant proteins which can be secreted in the animal's milk and then recovered.

[0335] A transgenic animal can be produced by introducing a SNP-containing nucleic acid molecule into the male pronuclei of a fertilized oocyte, e.g., by microinjection or retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any nucleic acid molecules that contain one or more SNPs described herein can potentially be introduced as a transgene into the genome of a non-human animal.

[0336] Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. This includes intronic sequences and polyadenylation signals, if not already included. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the variant protein in particular cells or tissues.

[0337] Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described in, for example, U.S. Patent Nos. 4,736,866 and

4,870,009, both by Leder et al., U.S. Patent No. 4,873,191 by Wagner et al., and in Hogan, B., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of transgenic mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene can further be bred to other transgenic animals carrying other transgenes. A transgenic animal also includes a non-human animal in which the entire animal or tissues in the animal have been produced using the homologously recombinant host cells described herein.

[0338] In another embodiment, transgenic non-human animals can be produced which contain selected systems that allow for regulated expression of the transgene. One example of such a system is the cre/loxP recombinase system of bacteriophage P1 (Lakso et al. PNAS 89:6232-6236 (1992)). Another example of a recombinase system is the FLP recombinase system of *S. cerevisiae* (O'Gorman et al. Science 251:1351-1355 (1991)). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are generally needed. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected variant protein and the other containing a transgene encoding a recombinase.

[0339] Clones of the non-human transgenic animals described herein can also be produced according to the methods described in, for example, Wilmut, I. et al. Nature 385:810-813 (1997) and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell (e.g., a somatic cell) from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyst and then transferred to pseudopregnant female foster animal. The offspring bom of this female foster animal will be a clone of the animal from which the cell (e.g., a somatic cell) is isolated.

[0340] Transgenic animals containing recombinant cells that express the variant proteins described herein are useful for conducting the assays described herein in an *in vivo* context. Accordingly, the various physiological factors that are present *in vivo* and that could influence ligand or substrate binding, variant protein activation, signal transduction, or other processes or interactions, may not be evident from *in vitro* cell-free or cell-based assays. Thus, non-human transgenic animals described herein may be used to assay *in vivo* variant protein function as well as the activities of a therapeutic agent or compound that modulates variant protein function/activity or expression. Such animals are also suitable for assessing the effects of null mutations (i.e., mutations that substantially or completely eliminate one or more variant protein functions).

[0341] For further information regarding transgenic animals, see Houdebine, "Antibody manufacture in transgenic animals and comparisons with other systems", Curr Opin Biotechnol. 2002 Dec;13(6):625-9; Petters et al., "Transgenic animals as models for human disease", Transgenic Res. 2000;9(4-5):347-51; discussion 345-6; Wolf et al., "Use of transgenic animals in understanding molecular mechanisms of toxicity", J Pharm Pharmacol. 1998 Jun;50(6):567-74; Echelard, "Recombinant protein production in transgenic animals", Curr Opin Biotechnol. 1996 Oct;7(5):536-40; Houdebine, "Transgenic animal bioreactors", Transgenic Res. 2000;9(4-5):305-20; Pirity et al., "Embryonic stem cells, creating transgenic animals", Methods Cell Biol. 1998;57:279-93; and Robl et al., "Artificial chromosome vectors and expression of complex proteins in transgenic animals", Theriogenology. 2003 Jan 1;59(1):107-13.

COMPUTER-RELATED EMBODIMENTS

[0342] The SNPs described herein may be "provided" in a variety of mediums to facilitate use thereof. As used in this section, "provided" refers to a manufacture, other than an isolated nucleic acid molecule, that contains SNP information described herein. Such a manufacture provides the SNP described herein in a form that allows a skilled artisan to examine the manufacture using means not directly applicable to examining the SNPs or a subset thereof as they exist in nature or in purified form. The SNP information that may be provided in such a form includes any of the SNP information described herein such as, for example, polymorphic nucleic acid and/or amino acid sequence information such as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:3, and SEQ ID NO:5; information about observed SNP alleles, alternative codons, populations, allele frequencies, SNP types, and/or affected proteins; or any other information provided by the present invention in Tables 1-2 and/or the Sequence Listing.

[0343] In one application of this embodiment, the SNPs described herein can be recorded on a computer readable medium. As used herein, "computer readable medium" refers to any medium that can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable media can be used to create a manufacture comprising computer readable

medium having recorded thereon a nucleotide sequence of the present invention. One such medium is a computer readable medium (CD-R) that has nucleic acid sequences (and encoded protein sequences) containing SNPs provided/recorded thereon in ASCII text format in a Sequence Listing along with accompanying Tables that contain detailed SNP and sequence information (transcript sequence is provided as SEQ ID NO:1, protein sequence is provided as SEQ ID NO:2, genomic sequence is provided as SEQ ID NO:4, transcript-based context sequence is provided as SEQ ID NO: 3, and genomic-based context sequence is provided as SEQ ID NO:5).

[0344] As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the SNP information described herein.

[0345] A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide or amino acid sequence described herein. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide/amino acid sequence information described herein on computer readable medium. For example, the sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, represented in the form of an ASCII file, or stored in a database application, such as OB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (e.g., text file or database) in order to obtain computer readable medium having recorded thereon the SNP information described herein.

[0346] By providing the SNPs described herein in computer readable form, a skilled artisan can routinely access the SNP information for a variety of purposes. Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium. Examples of publicly available computer software include BLAST (Altschul et at, J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et at, Comp. Chem. 17:203-207 (1993)) search algorithms.

[0347] Described herein are systems, particularly computer-based systems, which contain the SNP information described herein. Such systems may be designed to store and/or analyze information on, for example, a large number of SNP positions, or information on SNP genotypes from a large number of individuals. The SNP information described herein represents a valuable information source. The SNP information described herein stored/analyzed in a computer-based system may be used for such computer-intensive applications as determining or analyzing SNP allele frequencies in a population, mapping disease genes, genotype-phenotype association studies, grouping SNPs into haplotypes, correlating SNP haplotypes with response to particular drugs, or for various other bioinformatic, pharmacogenomic, drug development, or human identification/forensic applications.

[0348] As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the SNP information described herein. The minimum hardware means of the computer-based systems described herein typically comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the described system. Such a system can be changed into a system described herein by utilizing the SNP information provided, or a subset thereof, without any experimentation.

[0349] As stated above, the computer-based systems described herein comprise a data storage means having stored therein SNPs described herein and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store SNP information described herein, or a memory access means which can access manufactures having recorded thereon the SNP information described herein.

[0350] As used herein, "search means" refers to one or more programs or algorithms that are implemented on the computer-based system to identify or analyze SNPs in a target sequence based on the SNP information stored within the data storage means. Search means can be used to determine which nucleotide is present at a particular SNP position in the target sequence. As used herein, a "target sequence" can be any DNA sequence containing the SNP position(s) to be searched or queried.

[0351] As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences containing a SNP position in which the sequence(s) is chosen based on a three-dimensional configuration that is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzymatic active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures, and inducible expression elements (protein binding sequences).

[0352] A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention. An exemplary format for an output means is a display that depicts the presence or absence of specified nucleotides (alleles) at particular SNP positions of interest. Such presentation can provide a rapid, binary scoring system for many SNPs simultaneously.

[0353] One exemplary embodiment of a computer-based system comprising SNP information described herein is

provided in Figure 1. Figure 1 provides a block diagram of a computer system 102 that can be used to implement the present disclosure. The computer system 102 includes a processor 106 connected to a bus 104. Also connected to the bus 104 are a main memory 108 (preferably implemented as random access memory, RAM) and a variety of secondary storage devices 110, such as a bard drive 112 and a removable medium storage device 114. The removable medium storage device 114 may represent, for example, a floppy disk drive, a CD-ROM drive, a magnetic tape drive, etc. A removable storage medium 116 (such as a floppy disk, a compact disk, a magnetic tape, etc.) containing control logic and/or data recorded therein may be inserted into the removable medium storage device 114. The computer system 102 includes appropriate software for reading the control logic and/or the data from the removable storage medium 116 once inserted in the removable medium storage device 114.

[0354] The SNP information described herein may be stored in a well-known manner in the main memory 108, any of the secondary storage devices 110, and/or a removable storage medium 116. Software for accessing and processing the SNP information (such as SNP scoring tools, search tools, comparing tools, etc.) preferably resides in main memory 108 during execution.

EXAMPLES: STATISTICAL ANALYSIS OF SNP ASSOCIATION WITH MYOCARDIAL INFARCTION AND RECURRENT MYOCARDIAL INFARCTION

Myocardial Infarction studies

[0355] A case-control genetic study to determine the association of SNPs in the human genome with MI was carried out using genomic DNA extracted from 3 independently collected case-control sample sets.

[0356] Study S0012 had 1400 samples, in which patients (cases) had self-reported history of MI, and controls had no history of MI or of acute angina lasting more than 1 hour. Study S0028 had 1500 samples, in which patients (cases) had clinical evidence of history of MI, and controls had no history of MI. Study V0001 had 1288 samples, in which patients (cases) had clinical evidence of history of MI, and controls had no history of MI. All individuals who were included in each study had signed a written informed consent form. The study protocol was IRB approved.

[0357] DNA was extracted from blood samples using conventional DNA extraction methods such as the QIA-amp kit from Qiagen. SNP markers in the extracted DNA - were analyzed by genotyping. While some samples were individually genotyped, the same samples were also used for pooling studies, in which DNA from about 50 individuals was pooled, and allele frequencies were determined in pooled DNA. For studies S0012(M) and S0012(F), only male or female cases and controls were used in pooling studies. Genotypes and pool allele frequencies were obtained using a PRISM 7900HT sequence detection PCR system (Applied Biosystems, Foster City, CA) by allele-specific PCR, similar to the method described by Germer et al (Germer S., Holland M.J., Higuchi R. 2000, Genome Res. 10: 258-266). Primers for the allele-specific PCR reactions are provided in Table 5.

[0358] Summary statistics for demographic and environmental traits, history of vascular disease, and allele frequencies for the tested SNPs were obtained and compared between cases and controls. No multiple testing corrections were made.

[0359] Tests of association were calculated for both non-stratified and stratified settings: 1) Fisher's exact test of allelic association, and 2) asymptotic chi-square test of genotypic association, taking two different modes of inheritance into account (dominant, and recessive).

[0360] Effect sizes were estimated through allelic odds ratios, including 95% confidence intervals. The reported Allele1 may be under-represented in cases (with a lower allele frequency in cases than in controls, indicating that the reported Allele1 is associated with decreased risk and the other allele is a risk factor for disease) or over-represented in cases (indicating that the reported Allele1 is a risk factor in the development of disease).

[0361] A SNP was considered to be a significant genetic marker if it exhibited a p-value < 0.05 in the allelic association test or in any of the 2 genotypic tests (dominant, recessive). The association of a marker with MI was considered replicated if the marker exhibited an allelic or genotypic association test p-value <0.05 in one of the sample sets and the same test and strata (or substrata) were significant ($p<0.05$) in another independent sample set.

[0362] An example of a replicated marker, where the reported Allele1 is associated with decreased risk for MI, is hCV8851074 (Table 6). hCV8851074 shows significant association with all individuals (strata = "ALL") of study S0028 and the non-smoking strata (Stratification = "SMOKE", Strata = "N") of study S0012. The odds ratio in both studies is less than 1 (0.84 and 0.78 respectively), using the same allele (Allele1 = "A") for analysis.

[0363] An example of a replicated marker, where the reported Allele1 is associated with increased risk for MI, is hCV2716008 (Table 6). hCV2716008 shows significant association with all individuals (strata = "ALL") of study S0028 and all males of study S0012 (strata = "ALL", study="S0012(M)"). The odds ratio in both studies is greater than 1 (1.42 and 1.32 respectively), using the same allele (Allele1 = "C") for analysis.

Recurrent Myocardial Infarction (RMI) studies (see Table 7)

[0364] In order to identify genetic markers associated with recurrent myocardial infarction (RMI), samples from the Cholesterol and Recurrent Events (CARE) study were genotyped utilizing 864 assays for functional SNPs in 500 candidate genes. A well-documented MI was one of the enrollment criteria for the CARE study. Patients were followed up for 5 years and rates of recurrent MI were recorded in Pravastatin treated and placebo groups.

[0365] In the initial analysis (CARE), SNP genotype frequencies were compared in a group of 264 patients who had another MI (second, third, or fourth) during the 5 years of CARE follow-up (cases) versus the frequencies in the group of 1255 CARE patients who had not experienced a second MI (controls).

[0366] To replicate the initial findings, a second group of 394 CARE patients were analyzed who had a history of an MI prior to the MI at CARE enrollment but who had not experienced an MI during trial follow-up (cases), and 1221 CARE MI patients without a second MI were used as controls (Pre-CARE Study). No patients from the CARE Study were used in the Pre-CARE Study.

[0367] The SNPs replicated between CARE and Pre-CARE Studies were also tested for primary MI in study S0012 (UCSF). Study S0012 had 1400 samples. MI patients (cases) in this study had a self-reported history of MI, and controls had no history of MI or of acute angina lasting more than 1 hour. Allele frequencies in this study were detected in pooling experiments, in which DNA from about 50 individuals was pooled, and allele frequencies were determined in pooled DNA. For study S0012, only male cases and controls were used in pooling studies.

[0368] DNA was extracted from blood samples using conventional DNA extraction methods like the QIA-amp kit from Qiagen. Genotypes were obtained on a PRISM 7900HT sequence detection PCR system (Applied Biosystems) by allele-specific PCR, similar to the method described by Germer et al (Germer S., Holland M.J., Higuchi R. 2000, Genome Res. 10: 258-266). Primers for the allele-specific PCR reactions are provided in Table 5.

[0369] Statistical analysis was done using asymptotic chi square test for allelic, dominant, or recessive association, or Armitage trend test for additive genotypic association in the non-stratified as well as in the strata. Replicated SNPs are provided in Table 7. A SNP is considered replicated if the at-risk alleles in both sample sets are identical, the p-values are less than 0.05 in both sample sets, and the significant association is seen in the same stratum in both sets or one stratum is inclusive of the other.

[0370] Effect sizes were estimated through allelic odds ratios and odds ratios for dominant and recessive models, including 95% confidence intervals. Homogeneity of Cochran-Mantel-Haenszel odds ratios was tested across different strata using the Breslow-Day test. A SNP was considered to be a significant genetic marker if it exhibited a p-value < 0.05 in the allelic association test or in any of the 3 genotypic tests (dominant, recessive, additive). Haldane Odds Ratios were used if either case or control count was zero. SNPs with significant HWE violations in both cases and controls ($p<1x10^{-4}$ in both tests) were not considered for further analysis, since significant deviation from HWE in both cases and controls for individual markers can be indicative of genotyping errors. The association of a marker with RMI was considered replicated if the marker exhibits an allelic or genotypic association test p-value <0.05 in one of the sample sets and the same test and strata are significant ($p<0.05$) in either one or two other independent sample sets.

[0371] Although the invention has been described in connection with specific preferred embodiments and certain working examples, it should be understood that the invention should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention that are obvious to those skilled in the field of molecular biology, genetics and related fields are intended to be within the scope of the present teaching.

Table 1

Gene Number: 29 / Celera Gene: hCG17039 - 1145000146900401 / Celera Transcript: hCT8086 -145000146900402 / Public Transcript Accession: NM_004525 / Celera Protein: hCP35177 -197000064926039 / Public Protein Accession: NP_004516 / Gene Symbol: LRP2 / Protein Name: low density lipoprotein-related protein 2;GP330;MEGALIN;gp330 / Celera Genomic Axis: GA_x5YUV32W8UP(25077259..25307064) / Chromosome: Chr2 / OMIM number: 600073 / OMIM Information: LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 2;LRP2 / Transcript Sequence (SEQ ID NO:4) / / Context (SEQ ID NO:3) / Celera SNP ID: hCV16165996 / SNP Position Transcript: 12384 / SNP Source: Applera / Population (Allele,Count): african american(A,3|G,33) caucasian(A,5|G,35) total(A,8|G,68) / SNP Type: MISSENSE MUTATION / Protein Coding: SEQ ID NO:2, 4094, (K,AAG) (E,GAG) // SNP Source: dbSNP / Population(Allele,Count): no_pop(G,-|A,-) / SNP Type: MISSENSE MUTATION / Protein Coding: SEQ ID NO:2, 4094, (K,AAG) (E,GAG) /

Table 2

Gene Number: 29 // Celera Gene: hCG17039 - 145000146900401 / Gene Symbol: LRP2 / Protein Name: low density lipoprotein-related protein 2;GP330;MEGALIN;gp330 / Celera Genomic Axis: GA_x5YUV32W8UP(25071260.. 25313065) / Chromosome: Chr2 / OMIM number: 600073 / OMIM Information: LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 2;LRP2 / Genomic Sequence (SEQ ID NO:4) // Context (SEQ ID NO:5) / Celera SNP ID: hCV16165996 / SNP Position Genomic: 208593 / SNP Source: Applera / Population(Allele,Count): african american(A,3|G,33) caucasian(A,5|G,35) total(A,8|G,68) / SNP Type: MISSENSE MUTATION // SNP Source: dbSNP / Population(Allele,Count): no_pop(G,-|A,-) / SNP Type: MISSENSE MUTATION /

Table 5

hCV	Alleles	Sequence A (allele-specific primer)
hCV16165996	C/T	CTGAGGCCTATGTCCTC (SEQ ID NO:6)
		Sequence B (allele-specific primer)
		CTGAGGCCTATGTCCTT (SEQ ID NO: 7)
		Sequence C (common primer)
		AGCTCTCCTTTGTTGCTACTG (SEQ ID NO: 8)

Table 7

Gene	Marker	Sample Set	p-value	OR*	95% CI	case freq	control freq	Allele 1	mode	Strata
LRP2	hCV16165996	BMS_CARE	0.036433	0.1535	0.02047-1.151	0.0101	0.0623	T	Rec	BMI_TERTILE_3
LRP2	hCV16165996	BMS_CARE	0.011482	0.2448	0.07533-0.796	0.0197	0.0760	T	Rec	FMHX_CHD-0
LRP2	hCV16165996	BMS_CARE	0.041336	0.2476	0.05822-1.053	0.0168	0.0646	T	Rec	HYPERTEN_1
LRP2	hCV16165996	BMS_CARE	0.049657	0.4346	0.1848-1.022	0.0272	0.0603	T	Rec	MALE
LRP2	hCV16165996	BMS_CARE	0.021819	0.4087	0.18573-0.9	0.0276	0.0648	T	Rec	ALL
LRP2	hCV16165996	BMS_PRE-CARE	0.045253	0.3095	0.0923-1.038	0.0233	0.0714	T	Rec	AGE_TERTILE_2
LRP2	hCV16165996	BMS_PRE-CARE	0.038948	0.3702	0.13918-0.985	0.0289	0.0744	T	Rec	AGE_TERTILE_3
LRP2	hCV16165996	BMS_PRE-CARE	0.010388	0.1835	0.04315-0.781	0.0159	0.0808	T	Rec	BMI_TERTILE_2
LRP2	hCV16165996	BMS_PRE-CARE	0.034392	0.3384	0.11833-0.968	0.0204	0.0580	T	Rec	PREVASTATIN
LRP2	hCV16165996	BMS_PRE-CARE	0.028361	0.4124	0.18255-0.932	0.0385	0.0884	T	Rec	PLACEBO
LRP2	hCV16165996	BMS_PRE-CARE	0.003587	0.2734	0.10784-0.693	0.0236	0.0812	T	Rec	FMHX_CHD-0
LRP2	hCV16165996	BMS_PRE-CARE	0.004987	0.0972	0.01308-0.722	0.0073	0.0703	T	Rec	GLUCOSE_TERTILE_3
LRP2	hCV16165996	BMS_PRE-CARE	0.026662	0.3545	0.13642-0.921	0.0303	0.0810	T	Rec	HYPERTEN_1
LRP2	hCV16165996	BMS_PRE-CARE	0.036151	0.4065	0.17053-0.969	0.0282	0.0666	T	Rec	HYPERTEN_0
LRP2	hCV16165996	BMS_PRE-CARE	0.006692	0.4177	0.2182-0.8	0.0318	0.0729	T	Rec	MALE
LRP2	hCV16165996	BMS_PRE-CARE	0.002522	0.3843	0.20212-0.731	0.0291	0.0724	T	Rec	ALL

SEQUENCE LISTING

[0372]

<110> CELERA CORPORATION

<120> GENETIC POLYMORPHISMS ASSOCIATED WITH MYOCARDIAL INFARCTION, METHODS OF DETECTION AND USES THEREOF

<130> C100740PCEP

<140> EP 03800092.3
<141> 2003-12-22

<150> 60/434,778
<151> 2002-12-20

<150> 60/453,135
<151> 2003-03-10

<150> 60/466,412
<151> 2003-04-30

<150> 60/504,955
<151> 2003-09-23

<160> 8

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 15471
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(15471)
<223> n = A,T,C or G, or insertion/deletion polymorphism (see Tables 1-2)

<400> 1

```
gcagacctaa aggagcgttc gctagcagag gcgctgccgg tgcggtgtgc tacgcgcgcc 60
cacctcccgg ggaaggaacg gcgaggccgg ggaccgtcgc ggagatggat cgcgggccgg 120
cagcagtggc gtgcacgctg ctcctggctc tcgtcgcctg cctagcsccg gccagtggcc 180
aagaatgtga cagtgcgcat tttcgctgtg gaagtgggca ttgcatccct gcagactgga 240
ggtgtgatgg gaccaaagac tgttcagatg acgcggatga attggctgc gctgttgtga 300
cctgccagca gggctatttc aagtgccaga gtgagggaca atgcatcccc arctcctggg 360
tgtgtgacca agatcaagac tgtgatgatg gctcagatga acrtcaagat tgctcacaaa 420
gtacatgctc aagtcatcag ataacatgct ccaatggtca gtgtatccca agtgaataca 480
ggtgcgacca cgtcrgagac tgcccmgatg gagctgatga gaatgactgc cagtacccaa 540
catgtgagca gcttacttgt gacaatgggg cctgctataa caccagtcag aagtgtgatt 600
ggaaagttga ttgcagggac tcctcagatg aaatcaactg cactgagata tgcttgcaca 660
atgagttttc atgtggcaat ggagagtgta tccctcgtgc ttatgtctgt gaccatgaca 720
atgattgcca agacggcagt gaygaacatg cttgcaacta tccgacctgc ggtggttacc 780
agttcacttg ccccagtggc cgatgcattt atcaaaactg ggtttgtgat ggagaagatg 840
actgtaaaga taatggagat gaagatggat gtgaaagcsg tcctcatgat gttcataaat 900
gttccccaag agaatggtct tgcccagagt cgggacgatg catctccatt tataaagttt 960
gtgatgggat tttagattgc ccaggaagag aagatgaaaa caacactagt accggaaaat 1020
actgtagtat gactctgtgc tctgccttga actgccagta ccagtgccat gagacgccgt 1080
atggaggagc gtgtttttgt cccccaggtt atatcatcaa ccacaatgac agccgtacct 1140
gtgttgagtt tgatgattgc cagatatggg gaatttgtga ccagaagtgt gaaagccgac 1200
ctggccgtca cctgtgccac tgtgaagaag ggtatatctt ggagcgtgga cagtattgca 1260
aagctaatga ttcctttggc gaggcctcca ttatcttctc caatggtcgg gatttgttaa 1320
ttggtgatat tcatggaagg agcttccgga tcctagtgga gtctcagaat cgtggagtgg 1380
ccgtgggtgt ggctttccac tatcacctgc aaagagtttt ttggacagac accgtgcaaa 1440
ataaggtttt ttcagttgac attaatggtt taaatatcca agaggttctc aatgtttctg 1500
ttgaaacccc agagaacctg gctgtggact gggttaataa taaaatctat ctagtggaaa 1560
```

ccaaggtcaa ccgcatagat atggtaaatt tggatggaag ctatcgggtt acccttataa 1620
ctgaaaactt ggggcatcct agaggaattg ccgtggaccc aactgttggt tatttatttt 1680
tctcagattg ggagagcctt tctggggaac ctaagctgga aagggcattc atggatggca 1740
gcaaccgtaa agacttggtg aaaacaaagc tgggatggcc tgctggggta actctggata 1800
tgatatcgaa gcgtgtttac tgggttgact ctcggtttga ttacattgaa actgtaactt 1860
atgatggaat tcaaaggaag actgtagttc atggaggctc cctcattcct catccctttg 1920
gagtaagctt atttgaaggt caggtgttct ttacagattg gacaaagatg gccgtgctga 1980
aggcaaacaa gttcacagag accaacccac aagtgtacta ccaggcttcc ctgaggccct 2040
atggagtgac tgtttaccat tccctcagac agccctatgc taccaatccg tgtaaagata 2100
acaatggggr ctgtgagcag gtctgtgtyc tcagccacag aacagataat gatggtttgg 2160
gtttccgttg caagtgcaca ttcggcttcc aactggatac agatgagcgc cactgcattg 2220
ctgttcagaa tttcctcatt ttttcatccc aagttgctat tcgtgggatc ccgttcacct 2280
tgtctaccca ggaagatgtc atggttccag tttcggggaa tccttctttc tttgtcggga 2340
ttgattttga cgcccaggac agcactatct ttttttcaga tatgtcaaaa cacatgattt 2400
ttaagcaaaa gattgatggc acaggaagag aaattctcgc agctaacagg gtggaaaatg 2460
ttgaaagttt ggcttttgay tggatttcaa agaatctcta ttggacagac tctcattaca 2520
agagtatcag tgtcatgagg ctagctgata aaacgagacg cacrgtagtt cagtatttaa 2580
ataacccacg gtcggtggta gttcatcctt ttgccgggta tctattcttc actgattggt 2640
tccgtcctgc taaaattatg agagcatgga gtgacggatc tcacctcttg cctgtaataa 2700
acactactct tggatggccc aatggcttgg ccatcgattg ggctgcttca cgattgtact 2760
gggtagatgc ctattttgat aaaattgagc acagcacctt tgatggttta gacagaagaa 2820
gactgggccr tatagagcag atgacacatc cgtttggact tgccatcttt ggagagcatt 2880
tatttttac tgactggaga ctgggtgcca ttattcgagt caggaaagca gatggtggag 2940
aaatgacagt tatccgaagt ggcattgctt acatactgca tttgaaatcg tatgatgtca 3000
acatccagac tggttctaac gcctgtaatc aacccacgca tcctaacggt gactgcagcc 3060
acttctgctt cccggtgcca aatttccagc gagtgtgtgg gtgcccttat ggaatgaggc 3120
tggcttccaa tcacttgaca tgcgaggggg acccaacmaa tgaaccaccc acrgagcagt 3180
gtggcttatt ttccttcccc tgtaaaaatg gcagatgtgt gcccaattac tatctctgtg 3240
atggagtcga tgattgtcat gataacagtg atgagcaact atgtggcaca cttaataata 3300
cctgttcatc ttcggcgttc acctgtggcc atggggagtg cattcctgca camtggcgct 3360
gtgacaaacg caacgactgt gtggatggca gtgatgagca caactgcccc acccacgcac 3420
ctgcttcctg ccttgacacc caatacacct gtgataatca ccagtgtatc tcaaagaact 3480
gggtctgtga cacagacaat gattgtgggg atggatctga tgaaaagaac tgcaattcga 3540
cagagacatg ccaacctagt cagtttaatt gccccaatca tcgatgtatt gacctatcgt 3600
ttgtctgtga tggtgacaag gattgtgttg atggatctga tgaggttggt tgtgtattaa 3660
actgtactgc ttctcaattc aagtgtgcca gtggggataa atgtattggc gtcacaaatc 3720
gttgtgatgg tgtttttgat tgcagtgaca actcggatga agcrggctgt ccaaccaggc 3780
ctcctggtat gtgccactca gatgaatttc agtgccaaga agatggtatc tgcatcccga 3840
acttctggga atgtgatggg catccagact gcctctatgg atctgatgag cacaatgcct 3900
gtgtccccaa gacttgccct tcatcatatt tccactgtgm caacggaaac tgcatccaca 3960
gggcatggct ctgtgatcgg gacaatgact gcggggatat gagtgatgag aaggactgcc 4020
ctactcagcc ctttcgctgt cctagttggc aatggcagtg tcttggccat aacatctgtg 4080
tgaatctgag tgtagtgtgt gatggcatct ttgactgccc caatgggaca gatgagtccc 4140
cactttgcaa tgggaacagc tgctcagatt tcaatggtgg ttgtactcac gagtgtgttc 4200
aagagccctt tggggctaaa tgcctatgtc cattgggatt cttacttgcc aatgattcta 4260
agacctgtga agacatagat gaatgtgata ttctaggctc ttgtagccag cactgttaca 4320
atatgagagg ttctttccgs tgctcgtgtg atacaggcta catgttagaa agtgatggga 4380
ggacttgcaa agttacagca tctgagagtc tgctgttact tgtggcaagt cagaacaaaa 4440
ttattgcsga cagtgtcacc tcccaggtcc acaatatcta ttcattggtc gagaatggtt 4500
cttacattgt agctgttgat tttgattcaa ttagtggtcg tatcttttgg tctgatgcaa 4560
ctcagggtaa aacctggagt gcgtttcaaa atggaacgga cagaagagtg gtatttgaca 4620
gtagcatcat cttgactgaa actattgcaa tagattgggt aggtcgtaat ctttactgga 4680
cagactatgc tctggaaaca attgaagtct ccaaaattga tgggagccac aggactgtgc 4740
tgattagtaa aaacctaaca aatccaagag gactagcatt agatcccaga atgaatgagc 4800
atctactgtt ctggtctgac tggggccacc accctcgcat cgagcgagcc agcatggacg 4860
gcagcatgcg cactgtcatt gtccaggaca agatcttctg gccctgcggc ttaactattg 4920
actaccccaa cagactgctc tacttcatgg actcctatct tgattacatg gacttttgyg 4980
attataatgg acaccatcgg agacaggtga tagccagtga tttgattata cggcacccct 5040
atgccctaac tctctttgaa gactctgtgt actggactga ccgtgctact cgtcgggtta 5100
tgcgagccaa caagtggcat ggagggaacc agtcagttgt aatgtataat attcaatggc 5160
cccttgggat tgttgcggtt catccttcga aacaaccaaa ttcygtgaat ccatgtgcct 5220
tttcccgctg cagccatctc tgcctgcttt cctcacaggg gcctcatttt tactcctgtg 5280
tttgtccttc aggatggagt ctgtctcctg atctcctgaa ttgcttgaga gatgatcaac 5340
ctttcttaat aactgtaagg caacatataa tttttggaat ctcccttaat cctgaggtga 5400
agagcaatga tgctatggtc cccatagcag ggatacagaa tggtttagat gttgaatttg 5460

atgatgctga gcaatacatc tattgggttg aaaatccagg tgaaattcac agagtgaaga 5520
cagatggcac caacaggaca gtatttgctt ctatatctat ggtggggcct tctatgaacc 5580
tggccttaga ttggatttca agaaaccttt attctaccaa tcctagaact cagtcaatcg 5640
aggttttgac actccacgga gatatcagat acagaaaaac attgattgcc aatgatggga 5700
cagctcttgg agttggcttt ccaattggca taactgttga tcctgctcgt gggaagctgt 5760
actggtcaga ccaaggaact gacagtgggg ttcctgccaa gatcgscagt gctaacatgg 5820
atggcacatc tgtgaaaact ctctttactg ggaacctcga acacctggag tgtgtcactc 5880
ttgacatcga agagcagaaa ctctactggg cagtcactgg aagaggagtg attgaaagag 5940
gaaacgtgga tggaacagat cgratgatcc tggtacacca gctttcccac ccctggggaa 6000
ttgcagtcca tgattctttc ctttattata ctgatgaaca gtatgaggtc attgaaagag 6060
ttgataaggc cactggggcc aacaaaatag tcttgagaga taatgttcca aatctgaggg 6120
gtcttcaagt ttatcacara cgcaatgcyg ccgaatcctc aaatggctgt agcaacaaca 6180
tgaatgcctg tcagcagatt tgcctgcctr taccaggagg attgttttcc tgcgcctgtg 6240
ccactggatt taaactcaat cctgataatc ggtcctgctc tccatataac tctttcaytg 6300
ttgtttcaat gctgtctgca atcagaggct ttagcttgga attgtcagat cattcagaaa 6360
ccatggtgcc rgtggcaggc caaggacgaa acgcactgca tgtggatgtg gatgtgtcct 6420
ctggctttat ttattggtgt gattttagca gctcagtggc atctgataat gcgatccgta 6480
gaattaaacc agatggatct tctctgatga acattgtgac acatggaata ggagaaaatg 6540
gagtccgggg tattgcagtg gattgggtag caggaamtct ttatttcacc aatgcctttg 6600
tttctgaaac actgatagaa gttctgcgga tcaatactac ttaccgccgt gttcttctta 6660
aagtcacagt ggacatgcct aggcatattg ttgtagatcc caagaacaga tacctcttct 6720
gggctgacta tgggcagaga ccaaagattg agcgttcttt ccttgactgt accaatcgaa 6780
cagtgcttgt gtcagagggc attgtcacac cacggggctt ggcagtggac cgaagtgatg 6840
gctacgttta ttgggttgat gaytctttag atataattgc aaggattcgt atcaatggag 6900
agaactctga agtrattcgt tatggcagtc gttacccaac tccttatggc atcrctgttt 6960
ttgaaaattc tatcatatgg gtagatagga atttgaaaaa gatcttccaa gccagcaagg 7020
aaccagagaa cacagagcca cccacagtga taagagayaa tatcaactgg ctaagagatg 7080
tgaccatctt tgacaagcaa gtccagcccc ggtcaccagc agaggtcaac aacaaccctt 7140
gcttggaaaa caatggtggg tgctctcatc tctgctttgc tctgcctgga ttgcacaccc 7200
caaaatgtga ctgtgccttt gggaccctgc aaagtgatgg caagaattgt gccatttcaa 7260
cagaaaattt cctcatcttt gccttgtcta attccttgag aagcttacac ttggaccctg 7320
aaaaccatag cccacctttc caaacaataa atgtggraag aactgtcatg tctctagact 7380
atgacagtgt aagtgataga atctacttca cacaaaattt agcctctgga gttggacaga 7440
tttcctatgc caccctgtct tcagggatcc atactccaac tgtcattgct tcaggtatag 7500
ggactgctga tggcattgcc tttgactgga ttactagaag aatttattac agtgactacc 7560
tcaaccagat gattaattcc atggctgaag atgggtctaa ccgcactgtg atagcccgcg 7620
ttccaaaacc aagagcaatt gtgttagatc cctgccaagg gtacctgtac tgggctgact 7680
gggatacaca tgccaaaatc gagagagcca cattgggagg aaacttccgc gtacccattg 7740
tgaacagcag tctggtcatg cccagtgggc tgactctgga ctatgaagag gaccttctct 7800
actgggtgga tgctagtctg cagaggattg aacgcagcac tctgacgggc gtggatcgtg 7860
aagtcattgt caatgcagcc gttcatgctt ttggcttgac tctctatggc cagtatattt 7920
actggactga cttgtacaca caaagaattt accgagctaa caaatatgac gggtcaggtc 7980
agattgcaat gaccacarat ttgctctccc agcccagggg artcaacact gttgtgaaga 8040
accagaaaca acagtgtaac aatccttgtg aacagtttaa tgggggctgc agccatatct 8100
gtgcaccagg tccaaatggt gccgagtgcc agtgtccaca tgagggcaac tggtatttgg 8160
ccaacaacag gaagcactgc attgtggaca atggtgaacg atgtggtgca tcttccttca 8220
cctgctccaa tgggcgctgc atctcggaag agtggaagtg tgataatgac aacgactgtg 8280
gggatggcag tgatgagatg gaaagtgtct gtgcacttca cacctgctca ccgacagcct 8340
tcacctgtgc caatgggcga tgtgtccaat actcttaccg ctgtgattac tacaatgact 8400
gtggtgatgg cagtgatgag gcagggtgcc tgttcaggga ctgcaatgcc accacggagt 8460
ttatgtgcaa taacagaagg tgcatacctc gtgagtttat ctgcaatggt gtagacaact 8520
gccatgataa taacacttca gatgagaaaa attgccctga tcgcacttgc cagtctggat 8580
acacaaaatg tcataattca aatatttgta ttcctcgcgt ttatttgtgt gacggagaca 8640
atgactgtgg agataacagt gatgaaaacc ctacttattg caccactcac acgtgcagca 8700
gcagtgagtt ccaatgcnca tctgggcgct gtattcctca acattggtat tgtgatcaag 8760
aaacagattg ttttgatgcc tctgatgaac ctgcctcttg tggtcactct gagcgaacat 8820
gcctagctga tgagttcaag tgtgatggtg ggaggtgcat cccaagcgaa tggatctgtg 8880
acggtgataa tgactgtggg gatatgagtg acgaggataa aaggcaccag tgtcagaatc 8940
aaaactgctc ggattccgag tttctctgtg taaatgacag acctccggac aggaggtgca 9000
ttccccagtc ttgggtctgt gatggcgatg tggattgtac tgacggctac gatgagaatc 9060
agaattgcac caggagaact tgctctgaaa atgaattcac ctgtggttac ggactgtgta 9120
tcccaaagat attcaggtgt gaccggcaca atgactgtgg tgactatagc gacgagaggg 9180
gctgcttata ccagacttgc caacagaatc agtttacctg tcagaacggg cgctgcatta 9240
gtaaaacctt cgtctgtgat gaggataatg actgtggaga cggatctgat gagctgatgc 9300
acctgtgcca caccccagaa cccacgtgtc cacctcacga gttcaagtgt gacaatgggc 9360

gctgcatcga gatgatgaaa ctctgyaacc acctagatga ctgtttggac aacagcgatg 9420
agaaaggctg tggcattaat gaatgccatg acccttcaat cagtggctgc gatcacaact 9480
gcacagacac cttaaccagt ttctattgtt cctgtcrtcc tggttacaag ctcatgtctg 9540
acaagcggac ttgtgttgat attgatgaat gcacagagat gccttttgtc tgtagccaga 9600
agtgtgagaa tgtaataggc tcctacatct gtaagtgtgc cccaggctac ctccgagaac 9660
cagatggaaa gacctgccgg caaaacagta acatcgaacc ctatctcatt tttagcracc 9720
gttactattt gagaaattta actatagatg gctattttta ctccctcatc ttggaaggac 9780
tggacaatgt tgtggcatta gattttgacc gagtagagaa gagattgtat tggattgata 9840
cacagaggca agtcattgag agaatgtttc tgaataagac aaacaaggag acaatcataa 9900
accacagact accagctgca gaaagtctgg ctgtagactg ggtttccaga aagctctact 9960
ggttggatgc ccgcctggat ggcctctttg tctctgacct caatggtgga caccgccrca 10020
tgctggccca gcactgtgtg gatgccaaca acaccttctg ctttgataat cccagaggac 10080
ttgcccttca ccctcaatat gggtacctct actgggcaga ctggggtcac cgcgcataca 10140
ttgggagagt aggcatggat ggaaccaaca agtctgtgat aatctccacc aagttagagt 10200
ggcctaatgg catcaccatt gattacacca atgatctact ctactgggca gatgcccacc 10260
tgggttacat agagtactct gatttggagg gccaccatcg acacacggtg tatgatgggg 10320
cactgcctca ccctttcgct attaccattt ttgaagacac tatttattgg acagattgga 10380
atacaaggac agtggaaaag ggaaacaaat atgatggatc aaatagacag acactggtga 10440
acacaacaca cagaccattt gacatccatg tgtaccatcc atataggcag cccattgtga 10500
gcaatccctg tggtaccaac aatggtggct gttctcatct ctgcctcatc aagccaggag 10560
gaaaagggtt cacttgcgag tgtccagatg acttccgcac ccttcarctg agtggcagca 10620
cctactgcat gcccatgtgc tccagcaccc agttcctgtg cgctaacaat gaaaagtgca 10680
ttcctatctg gtggaaatgt gatggacaga aagactgctc agatggctct gatgaactgg 10740
ccctttgccc gcagcgcttc tgccgactgg gacagttcca gtgcagtgac ggcaactgca 10800
ccagcccgca gactttatgc aatgctcacc aaaattgccc tgatgggtct gatgaagacc 10860
gtcttctttg tgagaatcac cactgtgact ccaatgaatg gcagtgcgcc aacaaacgtt 10920
gcatcccaga atcctggcag tgtgacacat ttaacgactg tgaggataac tcagatgaag 10980
acagttccca ctgtgccagc aggacctgcc ggccgggcca gtttcggtgt gctaatggcc 11040
gctgcatccc gcaggcctgg aagtgtgatg tggataatga ttgtggagac cactcggatg 11100
agcccattga agaatgcatg agctctgccc atctctgtga caacttcaca gaattcagct 11160
gcaaaacaaa ttaccgctgc atcccaaagt gggccrtgtg caatggtgta gatgactgca 11220
gggacaacag tgatgagcaa ggctgtgagg agaggacatg ccatcctgtg ggggatttcc 11280
gctgtaaaaa tcaccactgc atccctcttc gttggcagtg tgatgggcaa aatgactgtg 11340
gagataactc agatgaggaa aactgtgctc cccgggagtg cacagagagc gagtttcgat 11400
gtgtcaatca gcagtgcatt ccctcgcgat ggatctgtga ccattacaac gactgtgggg 11460
acaactcaga tgaacgggac tgtgagatga ggacctgcca tcctgaatat tttcagtgta 11520
caagtggaca ttgtgtacac agtgaactga aatgcgatgg atccgctgac tgtttggatg 11580
cgtctgatga agctgattgt cccacacgct ttcctgatgg tgcatactgc caggctacta 11640
tgttcgaatg caaaaaccat gtttgtatcc cgccatattg gaaatgtgat ggcgatgatg 11700
actgyggcga tggttcagat gaagaacttc acctgtgctt ggatgttccc tgtaattcac 11760
caaaccgttt ccggtgtgac aacaatcgct gcatttatag tcatgaggtg tgcaatggtg 11820
tggatgactg tggagatgga actgatgaga cagaggagca ctgtagaaaa ccgaccccta 11880
aaccttgtac agaatatgaa tataagtgtg gcaatgggca ttgcattcca catgacaatg 11940
tgtgtgatga tgccgatgac tgtggtgact ggtccgatga actgggttgc aataaaggaa 12000
aagaaagaac atgtgctgaa aatatatgcg agcaaaattg tacccaatta aatgaaggag 12060
gatytatctg ctcctgtaca gctgggttcg aaaccaatgt ttttgacaga acctcctgtc 12120
tagatatcaa tgaatgtgaa caatttggga cttgtcccca gcactgcaga aataccaaag 12180
gaagttatga gtgtgtctgt gctgatggct tcacgtctat gagtgaccgc cctggaaaac 12240
gatgtgcagc tgagggtagc tctcctttgt tgctactgcc tgacaatgtc cgaattcgaa 12300
aatataatct ctcatctgag aggttctcag agtatcttca agatgaggaa tatatccaag 12360
ctgttgatta tgattgggat cccraggaca taggcctcag tgttgtgtat tacactgtgc 12420
gaggggaggg ctctaggttt ggtgctatca aacgtgccta catccccaac tttgaatccg 12480
gccgcaataa tcttgtgcag gaagttgacc tgaaactgaa ataygtaatg cagccagatg 12540
gaatagcagt ggactgggtt ggaaggcata tttactggtc agatgtcaag aataaacgca 12600
ttgaggtggc taaacttgat ggaaggtaca gaaagtggct gatttccact gacctggacc 12660
aaccagctgc tattgctgtg aatcccaaac tagggcttat gttctggact gactggggaa 12720
aggaacctaa amtcgagtct gcctggatga atggagagga ccgcaacatc ctggttttcg 12780
aggaccttgg ttggccaact ggcctttcta tcgattattt gaacaatgrc cgaatctact 12840
ggagtgactt caaggaggac gttattgaaa ccataaaata tgatgggact gataggagag 12900
tcattgcaaa ggaagcaatg aacccttaca gcctggacat ctttgaagac cagttatact 12960
ggatatctaa ggaaaaggga gaagtatgga aacaaaataa atttgggcaa ggaaagaaag 13020
agaaaacgct ggtagtgaac ccttggctca ctcaagttcg aatctttcat caactcagat 13080
acaataagtc agtgcccaac ctttgcaaac agatctgcag ccacctctgc cttctgagac 13140
ctggaggata cagctgtgcc tgtccccaag gctccagctt tatagagggg agcaccactg 13200
agtgtgatgc agccatygaa ctgcctatca acctgccccc cccatgcagg tgcatgcayg 13260

```
gaggaaattg ctattttgat gagactgacc tccccaaatg caagtgtcct agcggctaca 13320
ccggaaaata ttgtgaaatg gcgttttcaa aaggcatctc tccaggaaca accgcagtag 13380
ctgtgctgtt gacaatcctc ttgatcgtcg taattggagc tctggcaatt gcaggattct 13440
tccactatag aaggaccggc tccctttgc ctgctctgcc caagctgcca agcttaagca 13500
gtctcgtcaa gccctctgaa aatgggaatg gggtgacctt cagatcaggg gcagatctta 13560
acatggatat tggagtgtct ggttttggac ctgagactgc tattgacagg tcaatggcaa 13620
tgagtgaaga ctttgtcatg gaaatgggra agcagcccat aatatttgaa aacccaatgt 13680
actcagccag agacagtgct gtcaaagtgg ttcagccaat ccaggtgact gtatctgaaa 13740
atgtggataa taagaattat ggaagtccca taaacccttc tgagatagtt ccagagacaa 13800
acccaacttc accagctgct gatggaactc aggtgacaaa atggaatctc ttcaaacgaa 13860
aatctaaaca aactaccaac tttgaaaatc caatctatgc acagatrgag aacgagcaaa 13920
aggaaagtgt tgctgcgaca ccacctccat caccttcgct ccctgctaag cctaagcctc 13980
cttcgagaag agacccaact ccaacctatt ctgcaacaga agacactttt aaagacaccg 14040
caaatcttgt taaagaagac tctgaagtat agctatacca gctatttagg gaataattag 14100
aaacacactt ttgcacatat atttttaca aacagatgaa aaaagttaac attcagtact 14160
ttatgaaaaa aatatatttt tccctgtttg cctatagttg gaggtatcct gtgtgtcttt 14220
ttttacttat gccgtctcat atttttacaa ataattatca caatgtacta tatgtatatc 14280
tttgcactga agttgtctga aggtaatact ataaatatat tgtatatttg taaattttgg 14340
aaagattatc ctgttactga atttgctaat aaagatgtct gctgatttgg ttggtgatca 14400
ttatagtaaa tgatccaaca agaaaaggaa ttgactgggg acctttagcc gtgtctaaag 14460
aagaggcacc actcatattt cctataaaat tatctaggaa aggaatccag gccccgctct 14520
tgggtccatt tttacacatt agcacttaat taatgttcaa tattacatgt caatttgatt 14580
aatggctatg ttgatagggg ccactatgtg ttgtatagac atctggactt gactgtagac 14640
tcctcagata atacagaagg taggaaaagc aattcagttt ggcccttctg tgtgttggca 14700
ttgtctaacc agaactctct gtttcatgtg tgttctctca ctagctgcca agacaacatt 14760
tttatttgtg atgtctatga ggaaatccca tatcattaag tgccagtgtc ctgcattgag 14820
tttgtggtta attaaatgag ctcttctgct gatggaccct ggagcaattt ctcccctcac 14880
ctgacattca aggtggtcac ctgccctagt agttggagct cagtagctga atttctgaaa 14940
ccaaatctgt gtcttcataa aataaggtgc aaaaaaaaaa aataccagtt aagtaaagcc 15000
tcaactgggt ttttgtttct atgaaaatat cattataatc actatttatt tcctaagttg 15060
aacctgaata gaaagggaaa ccattcttat taagcttttt attaggccct gtggctaaat 15120
gtgtacattt atattaraat gtactgtaca gtccagatct tttctttaat tcttattggt 15180
ttttttttt ttttttttt tagagatgga gtcttgctat attgccaagg ctgatcttga 15240
agtcctgggc tcaagtgatc ctcccacctc agcctcctga gtggttgggg ttacgggcgt 15300
gagccactgt gcctggcttc cagctctcct cttaaatagt gggtatagtc tgcacaacag 15360
gaaccatggc aggaatatac actttcccat agcaaatagc atacctgact ctctgtgcta 15420
atattgcaca tttgttaaac aatgaatgaa dggatggatg gatggatgga t          15471
```

<210> 2
<211> 4655
<212> PRT
<213> Homo sapiens

<400> 2

```
Met Asp Arg Gly Pro Ala Ala Val Ala Cys Thr Leu Leu Leu Ala Leu
 1               5                  10                  15
Val Ala Cys Leu Ala Pro Ala Ser Gly Gln Glu Cys Asp Ser Ala His
            20                  25                  30
Phe Arg Cys Gly Ser Gly His Cys Ile Pro Ala Asp Trp Arg Cys Asp
        35                  40                  45
Gly Thr Lys Asp Cys Ser Asp Asp Ala Asp Glu Ile Gly Cys Ala Val
    50                  55                  60
Val Thr Cys Gln Gln Gly Tyr Phe Lys Cys Gln Ser Glu Gly Gln Cys
65                  70                  75                  80
Ile Pro Asn Ser Trp Val Cys Asp Gln Asp Gln Asp Cys Asp Asp Gly
                85                  90                  95
Ser Asp Glu Arg Gln Asp Cys Ser Gln Ser Thr Cys Ser Ser His Gln
            100                 105                 110
Ile Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp
        115                 120                 125
His Val Arg Asp Cys Pro Asp Gly Ala Asp Glu Asn Asp Cys Gln Tyr
    130                 135                 140
Pro Thr Cys Glu Gln Leu Thr Cys Asp Asn Gly Ala Cys Tyr Asn Thr
145                 150                 155                 160
```

```
Ser Gln Lys Cys Asp Trp Lys Val Asp Cys Arg Asp Ser Ser Asp Glu
                165                 170                 175
Ile Asn Cys Thr Glu Ile Cys Leu His Asn Glu Phe Ser Cys Gly Asn
            180                 185                 190
Gly Glu Cys Ile Pro Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys
        195                 200                 205
Gln Asp Gly Ser Asp Glu His Ala Cys Asn Tyr Pro Thr Cys Gly Gly
    210                 215                 220
Tyr Gln Phe Thr Cys Pro Ser Gly Arg Cys Ile Tyr Gln Asn Trp Val
225                 230                 235                 240
Cys Asp Gly Glu Asp Asp Cys Lys Asp Asn Gly Asp Glu Asp Gly Cys
                245                 250                 255
Glu Ser Gly Pro His Asp Val His Lys Cys Ser Pro Arg Glu Trp Ser
            260                 265                 270
Cys Pro Glu Ser Gly Arg Cys Ile Ser Ile Tyr Lys Val Cys Asp Gly
        275                 280                 285
Ile Leu Asp Cys Pro Gly Arg Glu Asp Glu Asn Asn Thr Ser Thr Gly
    290                 295                 300
Lys Tyr Cys Ser Met Thr Leu Cys Ser Ala Leu Asn Cys Gln Tyr Gln
305                 310                 315                 320
Cys His Glu Thr Pro Tyr Gly Gly Ala Cys Phe Cys Pro Pro Gly Tyr
                325                 330                 335
Ile Ile Asn His Asn Asp Ser Arg Thr Cys Val Glu Phe Asp Asp Cys
            340                 345                 350
Gln Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Ser Arg Pro Gly Arg
        355                 360                 365
His Leu Cys His Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln Tyr
    370                 375                 380
Cys Lys Ala Asn Asp Ser Phe Gly Glu Ala Ser Ile Ile Phe Ser Asn
385                 390                 395                 400
Gly Arg Asp Leu Leu Ile Gly Asp Ile His Gly Arg Ser Phe Arg Ile
                405                 410                 415
Leu Val Glu Ser Gln Asn Arg Gly Val Ala Val Gly Val Ala Phe His
            420                 425                 430
Tyr His Leu Gln Arg Val Phe Trp Thr Asp Thr Val Gln Asn Lys Val
        435                 440                 445
Phe Ser Val Asp Ile Asn Gly Leu Asn Ile Gln Glu Val Leu Asn Val
    450                 455                 460
Ser Val Glu Thr Pro Glu Asn Leu Ala Val Asp Trp Val Asn Asn Lys
465                 470                 475                 480
Ile Tyr Leu Val Glu Thr Lys Val Asn Arg Ile Asp Met Val Asn Leu
                485                 490                 495
Asp Gly Ser Tyr Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro
            500                 505                 510
Arg Gly Ile Ala Val Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp
        515                 520                 525
Trp Glu Ser Leu Ser Gly Glu Pro Lys Leu Glu Arg Ala Phe Met Asp
    530                 535                 540
Gly Ser Asn Arg Lys Asp Leu Val Lys Thr Lys Leu Gly Trp Pro Ala
545                 550                 555                 560
Gly Val Thr Leu Asp Met Ile Ser Lys Arg Val Tyr Trp Val Asp Ser
                565                 570                 575
Arg Phe Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys
            580                 585                 590
Thr Val Val His Gly Gly Ser Leu Ile Pro His Pro Phe Gly Val Ser
        595                 600                 605
Leu Phe Glu Gly Gln Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val
    610                 615                 620
Leu Lys Ala Asn Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr Tyr Gln
625                 630                 635                 640
Ala Ser Leu Arg Pro Tyr Gly Val Thr Val Tyr His Ser Leu Arg Gln
                645                 650                 655
Pro Tyr Ala Thr Asn Pro Cys Lys Asp Asn Asn Gly Gly Cys Glu Gln
            660                 665                 670
Val Cys Val Leu Ser His Arg Thr Asp Asn Asp Gly Leu Gly Phe Arg
```

675 680 685
Cys Lys Cys Thr Phe Gly Phe Gln Leu Asp Thr Asp Glu Arg His Cys
690 695 700
Ile Ala Val Gln Asn Phe Leu Ile Phe Ser Ser Gln Val Ala Ile Arg
705 710 715 720
Gly Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val
725 730 735
Ser Gly Asn Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln Asp
740 745 750
Ser Thr Ile Phe Phe Ser Asp Met Ser Lys His Met Ile Phe Lys Gln
755 760 765
Lys Ile Asp Gly Thr Gly Arg Glu Ile Leu Ala Ala Asn Arg Val Glu
770 775 780
Asn Val Glu Ser Leu Ala Phe Asp Trp Ile Ser Lys Asn Leu Tyr Trp
785 790 795 800
Thr Asp Ser His Tyr Lys Ser Ile Ser Val Met Arg Leu Ala Asp Lys
805 810 815
Thr Arg Arg Thr Val Val Gln Tyr Leu Asn Asn Pro Arg Ser Val Val
820 825 830
Val His Pro Phe Ala Gly Tyr Leu Phe Phe Thr Asp Trp Phe Arg Pro
835 840 845
Ala Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Leu Pro Val
850 855 860
Ile Asn Thr Thr Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ala
865 870 875 880
Ala Ser Arg Leu Tyr Trp Val Asp Ala Tyr Phe Asp Lys Ile Glu His
885 890 895
Ser Thr Phe Asp Gly Leu Asp Arg Arg Arg Leu Gly His Ile Glu Gln
900 905 910
Met Thr His Pro Phe Gly Leu Ala Ile Phe Gly Glu His Leu Phe Phe
915 920 925
Thr Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ala Asp Gly
930 935 940
Gly Glu Met Thr Val Ile Arg Ser Gly Ile Ala Tyr Ile Leu His Leu
945 950 955 960
Lys Ser Tyr Asp Val Asn Ile Gln Thr Gly Ser Asn Ala Cys Asn Gln
965 970 975
Pro Thr His Pro Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro
980 985 990
Asn Phe Gln Arg Val Cys Gly Cys Pro Tyr Gly Met Arg Leu Ala Ser
995 1000 1005
Asn His Leu Thr Cys Glu Gly Asp Pro Thr Asn Glu Pro Pro Thr Glu
1010 1015 1020
Gln Cys Gly Leu Phe Ser Phe Pro Cys Lys Asn Gly Arg Cys Val Pro
1025 1030 1035 1040
Asn Tyr Tyr Leu Cys Asp Gly Val Asp Asp Cys His Asp Asn Ser Asp
1045 1050 1055
Glu Gln Leu Cys Gly Thr Leu Asn Asn Thr Cys Ser Ser Ser Ala Phe
1060 1065 1070
Thr Cys Gly His Gly Glu Cys Ile Pro Ala His Trp Arg Cys Asp Lys
1075 1080 1085
Arg Asn Asp Cys Val Asp Gly Ser Asp Glu His Asn Cys Pro Thr His
1090 1095 1100
Ala Pro Ala Ser Cys Leu Asp Thr Gln Tyr Thr Cys Asp Asn His Gln
1105 1110 1115 1120
Cys Ile Ser Lys Asn Trp Val Cys Asp Thr Asp Asn Asp Cys Gly Asp
1125 1130 1135
Gly Ser Asp Glu Lys Asn Cys Asn Ser Thr Glu Thr Cys Gln Pro Ser
1140 1145 1150
Gln Phe Asn Cys Pro Asn His Arg Cys Ile Asp Leu Ser Phe Val Cys
1155 1160 1165
Asp Gly Asp Lys Asp Cys Val Asp Gly Ser Asp Glu Val Gly Cys Val
1170 1175 1180
Leu Asn Cys Thr Ala Ser Gln Phe Lys Cys Ala Ser Gly Asp Lys Cys
1185 1190 1195 1200

```
Ile Gly Val Thr Asn Arg Cys Asp Gly Val Phe Asp Cys Ser Asp Asn
                  1205                1210                1215
Ser Asp Glu Ala Gly Cys Pro Thr Arg Pro Pro Gly Met Cys His Ser
              1220                1225                1230
Asp Glu Phe Gln Cys Gln Glu Asp Gly Ile Cys Ile Pro Asn Phe Trp
          1235                1240                1245
Glu Cys Asp Gly His Pro Asp Cys Leu Tyr Gly Ser Asp Glu His Asn
      1250                1255                1260
Ala Cys Val Pro Lys Thr Cys Pro Ser Ser Tyr Phe His Cys Asp Asn
1265                1270                1275                1280
Gly Asn Cys Ile His Arg Ala Trp Leu Cys Asp Arg Asp Asn Asp Cys
                  1285                1290                1295
Gly Asp Met Ser Asp Glu Lys Asp Cys Pro Thr Gln Pro Phe Arg Cys
              1300                1305                1310
Pro Ser Trp Gln Trp Gln Cys Leu Gly His Asn Ile Cys Val Asn Leu
          1315                1320                1325
Ser Val Val Cys Asp Gly Ile Phe Asp Cys Pro Asn Gly Thr Asp Glu
      1330                1335                1340
Ser Pro Leu Cys Asn Gly Asn Ser Cys Ser Asp Phe Asn Gly Gly Cys
1345                1350                1355                1360
Thr His Glu Cys Val Gln Glu Pro Phe Gly Ala Lys Cys Leu Cys Pro
                  1365                1370                1375
Leu Gly Phe Leu Leu Ala Asn Asp Ser Lys Thr Cys Glu Asp Ile Asp
              1380                1385                1390
Glu Cys Asp Ile Leu Gly Ser Cys Ser Gln His Cys Tyr Asn Met Arg
          1395                1400                1405
Gly Ser Phe Arg Cys Ser Cys Asp Thr Gly Tyr Met Leu Glu Ser Asp
      1410                1415                1420
Gly Arg Thr Cys Lys Val Thr Ala Ser Glu Ser Leu Leu Leu Leu Val
1425                1430                1435                1440
Ala Ser Gln Asn Lys Ile Ile Ala Asp Ser Val Thr Ser Gln Val His
                  1445                1450                1455
Asn Ile Tyr Ser Leu Val Glu Asn Gly Ser Tyr Ile Val Ala Val Asp
              1460                1465                1470
Phe Asp Ser Ile Ser Gly Arg Ile Phe Trp Ser Asp Ala Thr Gln Gly
          1475                1480                1485
Lys Thr Trp Ser Ala Phe Gln Asn Gly Thr Asp Arg Arg Val Val Phe
      1490                1495                1500
Asp Ser Ser Ile Ile Leu Thr Glu Thr Ile Ala Ile Asp Trp Val Gly
1505                1510                1515                1520
Arg Asn Leu Tyr Trp Thr Asp Tyr Ala Leu Glu Thr Ile Glu Val Ser
                  1525                1530                1535
Lys Ile Asp Gly Ser His Arg Thr Val Leu Ile Ser Lys Asn Leu Thr
              1540                1545                1550
Asn Pro Arg Gly Leu Ala Leu Asp Pro Arg Met Asn Glu His Leu Leu
          1555                1560                1565
Phe Trp Ser Asp Trp Gly His His Pro Arg Ile Glu Arg Ala Ser Met
      1570                1575                1580
Asp Gly Ser Met Arg Thr Val Ile Val Gln Asp Lys Ile Phe Trp Pro
1585                1590                1595                1600
Cys Gly Leu Thr Ile Asp Tyr Pro Asn Arg Leu Leu Tyr Phe Met Asp
                  1605                1610                1615
Ser Tyr Leu Asp Tyr Met Asp Phe Cys Asp Tyr Asn Gly His His Arg
              1620                1625                1630
Arg Gln Val Ile Ala Ser Asp Leu Ile Ile Arg His Pro Tyr Ala Leu
          1635                1640                1645
Thr Leu Phe Glu Asp Ser Val Tyr Trp Thr Asp Arg Ala Thr Arg Arg
      1650                1655                1660
Val Met Arg Ala Asn Lys Trp His Gly Gly Asn Gln Ser Val Val Met
1665                1670                1675                1680
Tyr Asn Ile Gln Trp Pro Leu Gly Ile Val Ala Val His Pro Ser Lys
                  1685                1690                1695
Gln Pro Asn Ser Val Asn Pro Cys Ala Phe Ser Arg Cys Ser His Leu
              1700                1705                1710
Cys Leu Leu Ser Ser Gln Gly Pro His Phe Tyr Ser Cys Val Cys Pro
```

1715 1720 1725
Ser Gly Trp Ser Leu Ser Pro Asp Leu Leu Asn Cys Leu Arg Asp Asp
1730 1735 1740
Gln Pro Phe Leu Ile Thr Val Arg Gln His Ile Ile Phe Gly Ile Ser
1745 1750 1755 1760
Leu Asn Pro Glu Val Lys Ser Asn Asp Ala Met Val Pro Ile Ala Gly
1765 1770 1775
Ile Gln Asn Gly Leu Asp Val Glu Phe Asp Asp Ala Glu Gln Tyr Ile
1780 1785 1790
Tyr Trp Val Glu Asn Pro Gly Glu Ile His Arg Val Lys Thr Asp Gly
1795 1800 1805
Thr Asn Arg Thr Val Phe Ala Ser Ile Ser Met Val Gly Pro Ser Met
1810 1815 1820
Asn Leu Ala Leu Asp Trp Ile Ser Arg Asn Leu Tyr Ser Thr Asn Pro
1825 1830 1835 1840
Arg Thr Gln Ser Ile Glu Val Leu Thr Leu His Gly Asp Ile Arg Tyr
1845 1850 1855
Arg Lys Thr Leu Ile Ala Asn Asp Gly Thr Ala Leu Gly Val Gly Phe
1860 1865 1870
Pro Ile Gly Ile Thr Val Asp Pro Ala Arg Gly Lys Leu Tyr Trp Ser
1875 1880 1885
Asp Gln Gly Thr Asp Ser Gly Val Pro Ala Lys Ile Ala Ser Ala Asn
1890 1895 1900
Met Asp Gly Thr Ser Val Lys Thr Leu Phe Thr Gly Asn Leu Glu His
1905 1910 1915 1920
Leu Glu Cys Val Thr Leu Asp Ile Glu Glu Gln Lys Leu Tyr Trp Ala
1925 1930 1935
Val Thr Gly Arg Gly Val Ile Glu Arg Gly Asn Val Asp Gly Thr Asp
1940 1945 1950
Arg Met Ile Leu Val His Gln Leu Ser His Pro Trp Gly Ile Ala Val
1955 1960 1965
His Asp Ser Phe Leu Tyr Tyr Thr Asp Glu Gln Tyr Glu Val Ile Glu
1970 1975 1980
Arg Val Asp Lys Ala Thr Gly Ala Asn Lys Ile Val Leu Arg Asp Asn
1985 1990 1995 2000
Val Pro Asn Leu Arg Gly Leu Gln Val Tyr His Arg Arg Asn Ala Ala
2005 2010 2015
Glu Ser Ser Asn Gly Cys Ser Asn Asn Met Asn Ala Cys Gln Gln Ile
2020 2025 2030
Cys Leu Pro Val Pro Gly Gly Leu Phe Ser Cys Ala Cys Ala Thr Gly
2035 2040 2045
Phe Lys Leu Asn Pro Asp Asn Arg Ser Cys Ser Pro Tyr Asn Ser Phe
2050 2055 2060
Ile Val Val Ser Met Leu Ser Ala Ile Arg Gly Phe Ser Leu Glu Leu
2065 2070 2075 2080
Ser Asp His Ser Glu Thr Met Val Pro Val Ala Gly Gln Gly Arg Asn
2085 2090 2095
Ala Leu His Val Asp Val Asp Val Ser Ser Gly Phe Ile Tyr Trp Cys
2100 2105 2110
Asp Phe Ser Ser Ser Val Ala Ser Asp Asn Ala Ile Arg Arg Ile Lys
2115 2120 2125
Pro Asp Gly Ser Ser Leu Met Asn Ile Val Thr His Gly Ile Gly Glu
2130 2135 2140
Asn Gly Val Arg Gly Ile Ala Val Asp Trp Val Ala Gly Asn Leu Tyr
2145 2150 2155 2160
Phe Thr Asn Ala Phe Val Ser Glu Thr Leu Ile Glu Val Leu Arg Ile
2165 2170 2175
Asn Thr Thr Tyr Arg Arg Val Leu Leu Lys Val Thr Val Asp Met Pro
2180 2185 2190
Arg His Ile Val Val Asp Pro Lys Asn Arg Tyr Leu Phe Trp Ala Asp
2195 2200 2205
Tyr Gly Gln Arg Pro Lys Ile Glu Arg Ser Phe Leu Asp Cys Thr Asn
2210 2215 2220
Arg Thr Val Leu Val Ser Glu Gly Ile Val Thr Pro Arg Gly Leu Ala
2225 2230 2235 2240

```
Val Asp Arg Ser Asp Gly Tyr Val Tyr Trp Val Asp Asp Ser Leu Asp
                2245                2250                2255
Ile Ile Ala Arg Ile Arg Ile Asn Gly Glu Asn Ser Glu Val Ile Arg
            2260                2265                2270
Tyr Gly Ser Arg Tyr Pro Thr Pro Tyr Gly Ile Thr Val Phe Glu Asn
        2275                2280                2285
Ser Ile Ile Trp Val Asp Arg Asn Leu Lys Lys Ile Phe Gln Ala Ser
    2290                2295                2300
Lys Glu Pro Glu Asn Thr Glu Pro Pro Thr Val Ile Arg Asp Asn Ile
2305                2310                2315                2320
Asn Trp Leu Arg Asp Val Thr Ile Phe Asp Lys Gln Val Gln Pro Arg
                2325                2330                2335
Ser Pro Ala Glu Val Asn Asn Asn Pro Cys Leu Glu Asn Asn Gly Gly
            2340                2345                2350
Cys Ser His Leu Cys Phe Ala Leu Pro Gly Leu His Thr Pro Lys Cys
        2355                2360                2365
Asp Cys Ala Phe Gly Thr Leu Gln Ser Asp Gly Lys Asn Cys Ala Ile
    2370                2375                2380
Ser Thr Glu Asn Phe Leu Ile Phe Ala Leu Ser Asn Ser Leu Arg Ser
2385                2390                2395                2400
Leu His Leu Asp Pro Glu Asn His Ser Pro Pro Phe Gln Thr Ile Asn
                2405                2410                2415
Val Glu Arg Thr Val Met Ser Leu Asp Tyr Asp Ser Val Ser Asp Arg
            2420                2425                2430
Ile Tyr Phe Thr Gln Asn Leu Ala Ser Gly Val Gly Gln Ile Ser Tyr
        2435                2440                2445
Ala Thr Leu Ser Ser Gly Ile His Thr Pro Thr Val Ile Ala Ser Gly
    2450                2455                2460
Ile Gly Thr Ala Asp Gly Ile Ala Phe Asp Trp Ile Thr Arg Arg Ile
2465                2470                2475                2480
Tyr Tyr Ser Asp Tyr Leu Asn Gln Met Ile Asn Ser Met Ala Glu Asp
                2485                2490                2495
Gly Ser Asn Arg Thr Val Ile Ala Arg Val Pro Lys Pro Arg Ala Ile
            2500                2505                2510
Val Leu Asp Pro Cys Gln Gly Tyr Leu Tyr Trp Ala Asp Trp Asp Thr
        2515                2520                2525
His Ala Lys Ile Glu Arg Ala Thr Leu Gly Gly Asn Phe Arg Val Pro
    2530                2535                2540
Ile Val Asn Ser Ser Leu Val Met Pro Ser Gly Leu Thr Leu Asp Tyr
2545                2550                2555                2560
Glu Glu Asp Leu Leu Tyr Trp Val Asp Ala Ser Leu Gln Arg Ile Glu
                2565                2570                2575
Arg Ser Thr Leu Thr Gly Val Asp Arg Glu Val Ile Val Asn Ala Ala
            2580                2585                2590
Val His Ala Phe Gly Leu Thr Leu Tyr Gly Gln Tyr Ile Tyr Trp Thr
        2595                2600                2605
Asp Leu Tyr Thr Gln Arg Ile Tyr Arg Ala Asn Lys Tyr Asp Gly Ser
    2610                2615                2620
Gly Gln Ile Ala Met Thr Thr Asn Leu Leu Ser Gln Pro Arg Gly Ile
2625                2630                2635                2640
Asn Thr Val Val Lys Asn Gln Lys Gln Gln Cys Asn Asn Pro Cys Glu
                2645                2650                2655
Gln Phe Asn Gly Gly Cys Ser His Ile Cys Ala Pro Gly Pro Asn Gly
            2660                2665                2670
Ala Glu Cys Gln Cys Pro His Glu Gly Asn Trp Tyr Leu Ala Asn Asn
        2675                2680                2685
Arg Lys His Cys Ile Val Asp Asn Gly Glu Arg Cys Gly Ala Ser Ser
    2690                2695                2700
Phe Thr Cys Ser Asn Gly Arg Cys Ile Ser Glu Glu Trp Lys Cys Asp
2705                2710                2715                2720
Asn Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu Met Glu Ser Val Cys
                2725                2730                2735
Ala Leu His Thr Cys Ser Pro Thr Ala Phe Thr Cys Ala Asn Gly Arg
            2740                2745                2750
Cys Val Gln Tyr Ser Tyr Arg Cys Asp Tyr Tyr Asn Asp Cys Gly Asp
```

2755 2760 2765
Gly Ser Asp Glu Ala Gly Cys Leu Phe Arg Asp Cys Asn Ala Thr Thr
2770 2775 2780
Glu Phe Met Cys Asn Asn Arg Arg Cys Ile Pro Arg Glu Phe Ile Cys
2785 2790 2795 2800
Asn Gly Val Asp Asn Cys His Asp Asn Asn Thr Ser Asp Glu Lys Asn
2805 2810 2815
Cys Pro Asp Arg Thr Cys Gln Ser Gly Tyr Thr Lys Cys His Asn Ser
2820 2825 2830
Asn Ile Cys Ile Pro Arg Val Tyr Leu Cys Asp Gly Asp Asn Asp Cys
2835 2840 2845
Gly Asp Asn Ser Asp Glu Asn Pro Thr Tyr Cys Thr Thr His Thr Cys
2850 2855 2860
Ser Ser Ser Glu Phe Gln Cys Ala Ser Gly Arg Cys Ile Pro Gln His
2865 2870 2875 2880
Trp Tyr Cys Asp Gln Glu Thr Asp Cys Phe Asp Ala Ser Asp Glu Pro
2885 2890 2895
Ala Ser Cys Gly His Ser Glu Arg Thr Cys Leu Ala Asp Glu Phe Lys
2900 2905 2910
Cys Asp Gly Gly Arg Cys Ile Pro Ser Glu Trp Ile Cys Asp Gly Asp
2915 2920 2925
Asn Asp Cys Gly Asp Met Ser Asp Glu Asp Lys Arg His Gln Cys Gln
2930 2935 2940
Asn Gln Asn Cys Ser Asp Ser Glu Phe Leu Cys Val Asn Asp Arg Pro
2945 2950 2955 2960
Pro Asp Arg Arg Cys Ile Pro Gln Ser Trp Val Cys Asp Gly Asp Val
2965 2970 2975
Asp Cys Thr Asp Gly Tyr Asp Glu Asn Gln Asn Cys Thr Arg Arg Thr
2980 2985 2990
Cys Ser Glu Asn Glu Phe Thr Cys Gly Tyr Gly Leu Cys Ile Pro Lys
2995 3000 3005
Ile Phe Arg Cys Asp Arg His Asn Asp Cys Gly Asp Tyr Ser Asp Glu
3010 3015 3020
Arg Gly Cys Leu Tyr Gln Thr Cys Gln Gln Asn Gln Phe Thr Cys Gln
3025 3030 3035 3040
Asn Gly Arg Cys Ile Ser Lys Thr Phe Val Cys Asp Glu Asp Asn Asp
3045 3050 3055
Cys Gly Asp Gly Ser Asp Glu Leu Met His Leu Cys His Thr Pro Glu
3060 3065 3070
Pro Thr Cys Pro Pro His Glu Phe Lys Cys Asp Asn Gly Arg Cys Ile
3075 3080 3085
Glu Met Met Lys Leu Cys Asn His Leu Asp Asp Cys Leu Asp Asn Ser
3090 3095 3100
Asp Glu Lys Gly Cys Gly Ile Asn Glu Cys His Asp Pro Ser Ile Ser
3105 3110 3115 3120
Gly Cys Asp His Asn Cys Thr Asp Thr Leu Thr Ser Phe Tyr Cys Ser
3125 3130 3135
Cys Arg Pro Gly Tyr Lys Leu Met Ser Asp Lys Arg Thr Cys Val Asp
3140 3145 3150
Ile Asp Glu Cys Thr Glu Met Pro Phe Val Cys Ser Gln Lys Cys Glu
3155 3160 3165
Asn Val Ile Gly Ser Tyr Ile Cys Lys Cys Ala Pro Gly Tyr Leu Arg
3170 3175 3180
Glu Pro Asp Gly Lys Thr Cys Arg Gln Asn Ser Asn Ile Glu Pro Tyr
3185 3190 3195 3200
Leu Ile Phe Ser Asn Arg Tyr Tyr Leu Arg Asn Leu Thr Ile Asp Gly
3205 3210 3215
Tyr Phe Tyr Ser Leu Ile Leu Glu Gly Leu Asp Asn Val Val Ala Leu
3220 3225 3230
Asp Phe Asp Arg Val Glu Lys Arg Leu Tyr Trp Ile Asp Thr Gln Arg
3235 3240 3245
Gln Val Ile Glu Arg Met Phe Leu Asn Lys Thr Asn Lys Glu Thr Ile
3250 3255 3260
Ile Asn His Arg Leu Pro Ala Ala Glu Ser Leu Ala Val Asp Trp Val
3265 3270 3275 3280

Ser Arg Lys Leu Tyr Trp Leu Asp Ala Arg Leu Asp Gly Leu Phe Val
3285 3290 3295
Ser Asp Leu Asn Gly Gly His Arg Arg Met Leu Ala Gln His Cys Val
3300 3305 3310
Asp Ala Asn Asn Thr Phe Cys Phe Asp Asn Pro Arg Gly Leu Ala Leu
3315 3320 3325
His Pro Gln Tyr Gly Tyr Leu Tyr Trp Ala Asp Trp Gly His Arg Ala
3330 3335 3340
Tyr Ile Gly Arg Val Gly Met Asp Gly Thr Asn Lys Ser Val Ile Ile
3345 3350 3355 3360
Ser Thr Lys Leu Glu Trp Pro Asn Gly Ile Thr Ile Asp Tyr Thr Asn
3365 3370 3375
Asp Leu Leu Tyr Trp Ala Asp Ala His Leu Gly Tyr Ile Glu Tyr Ser
3380 3385 3390
Asp Leu Glu Gly His His Arg His Thr Val Tyr Asp Gly Ala Leu Pro
3395 3400 3405
His Pro Phe Ala Ile Thr Ile Phe Glu Asp Thr Ile Tyr Trp Thr Asp
3410 3415 3420
Trp Asn Thr Arg Thr Val Glu Lys Gly Asn Lys Tyr Asp Gly Ser Asn
3425 3430 3435 3440
Arg Gln Thr Leu Val Asn Thr Thr His Arg Pro Phe Asp Ile His Val
3445 3450 3455
Tyr His Pro Tyr Arg Gln Pro Ile Val Ser Asn Pro Cys Gly Thr Asn
3460 3465 3470
Asn Gly Gly Cys Ser His Leu Cys Leu Ile Lys Pro Gly Gly Lys Gly
3475 3480 3485
Phe Thr Cys Glu Cys Pro Asp Asp Phe Arg Thr Leu Gln Leu Ser Gly
3490 3495 3500
Ser Thr Tyr Cys Met Pro Met Cys Ser Ser Thr Gln Phe Leu Cys Ala
3505 3510 3515 3520
Asn Asn Glu Lys Cys Ile Pro Ile Trp Trp Lys Cys Asp Gly Gln Lys
3525 3530 3535
Asp Cys Ser Asp Gly Ser Asp Glu Leu Ala Leu Cys Pro Gln Arg Phe
3540 3545 3550
Cys Arg Leu Gly Gln Phe Gln Cys Ser Asp Gly Asn Cys Thr Ser Pro
3555 3560 3565
Gln Thr Leu Cys Asn Ala His Gln Asn Cys Pro Asp Gly Ser Asp Glu
3570 3575 3580
Asp Arg Leu Leu Cys Glu Asn His His Cys Asp Ser Asn Glu Trp Gln
3585 3590 3595 3600
Cys Ala Asn Lys Arg Cys Ile Pro Glu Ser Trp Gln Cys Asp Thr Phe
3605 3610 3615
Asn Asp Cys Glu Asp Asn Ser Asp Glu Asp Ser Ser His Cys Ala Ser
3620 3625 3630
Arg Thr Cys Arg Pro Gly Gln Phe Arg Cys Ala Asn Gly Arg Cys Ile
3635 3640 3645
Pro Gln Ala Trp Lys Cys Asp Val Asp Asn Asp Cys Gly Asp His Ser
3650 3655 3660
Asp Glu Pro Ile Glu Glu Cys Met Ser Ser Ala His Leu Cys Asp Asn
3665 3670 3675 3680
Phe Thr Glu Phe Ser Cys Lys Thr Asn Tyr Arg Cys Ile Pro Lys Trp
3685 3690 3695
Ala Val Cys Asn Gly Val Asp Asp Cys Arg Asp Asn Ser Asp Glu Gln
3700 3705 3710
Gly Cys Glu Glu Arg Thr Cys His Pro Val Gly Asp Phe Arg Cys Lys
3715 3720 3725
Asn His His Cys Ile Pro Leu Arg Trp Gln Cys Asp Gly Gln Asn Asp
3730 3735 3740
Cys Gly Asp Asn Ser Asp Glu Glu Asn Cys Ala Pro Arg Glu Cys Thr
3745 3750 3755 3760
Glu Ser Glu Phe Arg Cys Val Asn Gln Gln Cys Ile Pro Ser Arg Trp
3765 3770 3775
Ile Cys Asp His Tyr Asn Asp Cys Gly Asp Asn Ser Asp Glu Arg Asp
3780 3785 3790
Cys Glu Met Arg Thr Cys His Pro Glu Tyr Phe Gln Cys Thr Ser Gly

```
        3795                3800                3805
His Cys Val His Ser Glu Leu Lys Cys Asp Gly Ser Ala Asp Cys Leu
    3810                3815                3820
Asp Ala Ser Asp Glu Ala Asp Cys Pro Thr Arg Phe Pro Asp Gly Ala
3825                3830                3835                3840
Tyr Cys Gln Ala Thr Met Phe Glu Cys Lys Asn His Val Cys Ile Pro
                3845                3850                3855
Pro Tyr Trp Lys Cys Asp Gly Asp Asp Asp Cys Gly Asp Gly Ser Asp
            3860                3865                3870
Glu Glu Leu His Leu Cys Leu Asp Val Pro Cys Asn Ser Pro Asn Arg
        3875                3880                3885
Phe Arg Cys Asp Asn Asn Arg Cys Ile Tyr Ser His Glu Val Cys Asn
    3890                3895                3900
Gly Val Asp Asp Cys Gly Asp Gly Thr Asp Glu Thr Glu Glu His Cys
3905                3910                3915                3920
Arg Lys Pro Thr Pro Lys Pro Cys Thr Glu Tyr Glu Tyr Lys Cys Gly
                3925                3930                3935
Asn Gly His Cys Ile Pro His Asp Asn Val Cys Asp Asp Ala Asp Asp
            3940                3945                3950
Cys Gly Asp Trp Ser Asp Glu Leu Gly Cys Asn Lys Gly Lys Glu Arg
        3955                3960                3965
Thr Cys Ala Glu Asn Ile Cys Glu Gln Asn Cys Thr Gln Leu Asn Glu
    3970                3975                3980
Gly Gly Phe Ile Cys Ser Cys Thr Ala Gly Phe Glu Thr Asn Val Phe
3985                3990                3995                4000
Asp Arg Thr Ser Cys Leu Asp Ile Asn Glu Cys Glu Gln Phe Gly Thr
                4005                4010                4015
Cys Pro Gln His Cys Arg Asn Thr Lys Gly Ser Tyr Glu Cys Val Cys
            4020                4025                4030
Ala Asp Gly Phe Thr Ser Met Ser Asp Arg Pro Gly Lys Arg Cys Ala
        4035                4040                4045
Ala Glu Gly Ser Ser Pro Leu Leu Leu Leu Pro Asp Asn Val Arg Ile
    4050                4055                4060
Arg Lys Tyr Asn Leu Ser Ser Glu Arg Phe Ser Glu Tyr Leu Gln Asp
4065                4070                4075                4080
Glu Glu Tyr Ile Gln Ala Val Asp Tyr Asp Trp Asp Pro Glu Asp Ile
                4085                4090                4095
Gly Leu Ser Val Val Tyr Tyr Thr Val Arg Gly Glu Gly Ser Arg Phe
            4100                4105                4110
Gly Ala Ile Lys Arg Ala Tyr Ile Pro Asn Phe Glu Ser Gly Arg Asn
        4115                4120                4125
Asn Leu Val Gln Glu Val Asp Leu Lys Leu Lys Tyr Val Met Gln Pro
    4130                4135                4140
Asp Gly Ile Ala Val Asp Trp Val Gly Arg His Ile Tyr Trp Ser Asp
4145                4150                4155                4160
Val Lys Asn Lys Arg Ile Glu Val Ala Lys Leu Asp Gly Arg Tyr Arg
                4165                4170                4175
Lys Trp Leu Ile Ser Thr Asp Leu Asp Gln Pro Ala Ala Ile Ala Val
            4180                4185                4190
Asn Pro Lys Leu Gly Leu Met Phe Trp Thr Asp Trp Gly Lys Glu Pro
        4195                4200                4205
Lys Leu Glu Ser Ala Trp Met Asn Gly Glu Asp Arg Asn Ile Leu Val
    4210                4215                4220
Phe Glu Asp Leu Gly Trp Pro Thr Gly Leu Ser Ile Asp Tyr Leu Asn
4225                4230                4235                4240
Asn Asp Arg Ile Tyr Trp Ser Asp Phe Lys Glu Asp Val Ile Glu Thr
                4245                4250                4255
Ile Lys Tyr Asp Gly Thr Asp Arg Arg Val Ile Ala Lys Glu Ala Met
            4260                4265                4270
Asn Pro Tyr Ser Leu Asp Ile Phe Glu Asp Gln Leu Tyr Trp Ile Ser
        4275                4280                4285
Lys Glu Lys Gly Glu Val Trp Lys Gln Asn Lys Phe Gly Gln Gly Lys
    4290                4295                4300
Lys Glu Lys Thr Leu Val Val Asn Pro Trp Leu Thr Gln Val Arg Ile
4305                4310                4315                4320
```

```
Phe His Gln Leu Arg Tyr Asn Lys Ser Val Pro Asn Leu Cys Lys Gln
                4325                4330                4335
Ile Cys Ser His Leu Cys Leu Leu Arg Pro Gly Gly Tyr Ser Cys Ala
            4340                4345                4350
Cys Pro Gln Gly Ser Ser Phe Ile Glu Gly Ser Thr Thr Glu Cys Asp
        4355                4360                4365
Ala Ala Ile Glu Leu Pro Ile Asn Leu Pro Pro Pro Cys Arg Cys Met
    4370                4375                4380
His Gly Gly Asn Cys Tyr Phe Asp Glu Thr Asp Leu Pro Lys Cys Lys
4385                4390                4395                4400
Cys Pro Ser Gly Tyr Thr Gly Lys Tyr Cys Glu Met Ala Phe Ser Lys
                4405                4410                4415
Gly Ile Ser Pro Gly Thr Thr Ala Val Ala Val Leu Leu Thr Ile Leu
            4420                4425                4430
Leu Ile Val Val Ile Gly Ala Leu Ala Ile Ala Gly Phe Phe His Tyr
        4435                4440                4445
Arg Arg Thr Gly Ser Leu Leu Pro Ala Leu Pro Lys Leu Pro Ser Leu
    4450                4455                4460
Ser Ser Leu Val Lys Pro Ser Glu Asn Gly Asn Gly Val Thr Phe Arg
4465                4470                4475                4480
Ser Gly Ala Asp Leu Asn Met Asp Ile Gly Val Ser Gly Phe Gly Pro
                4485                4490                4495
Glu Thr Ala Ile Asp Arg Ser Met Ala Met Ser Glu Asp Phe Val Met
            4500                4505                4510
Glu Met Gly Lys Gln Pro Ile Ile Phe Glu Asn Pro Met Tyr Ser Ala
        4515                4520                4525
Arg Asp Ser Ala Val Lys Val Val Gln Pro Ile Gln Val Thr Val Ser
    4530                4535                4540
Glu Asn Val Asp Asn Lys Asn Tyr Gly Ser Pro Ile Asn Pro Ser Glu
4545                4550                4555                4560
Ile Val Pro Glu Thr Asn Pro Thr Ser Pro Ala Ala Asp Gly Thr Gln
                4565                4570                4575
Val Thr Lys Trp Asn Leu Phe Lys Arg Lys Ser Lys Gln Thr Thr Asn
            4580                4585                4590
Phe Glu Asn Pro Ile Tyr Ala Gln Met Glu Asn Glu Gln Lys Glu Ser
        4595                4600                4605
Val Ala Ala Thr Pro Pro Pro Ser Pro Ser Leu Pro Ala Lys Pro Lys
    4610                4615                4620
Pro Pro Ser Arg Arg Asp Pro Thr Pro Thr Tyr Ser Ala Thr Glu Asp
4625                4630                4635                4640
Thr Phe Lys Asp Thr Ala Asn Leu Val Lys Glu Asp Ser Glu Val
```

<210> 3
<211> 201
<212> DNA
<213> Homo sapiens

<400> 3

```
caatgtccga attcgaaaat ataatctctc atctgagagg ttctcagagt atcttcaaga 60
tgaggaatat atccaagctg ttgattatga ttgggatccc raggacatag gcctcagtgt 120
tgtgtattac actgtgcgag gggagggctc taggtttggt gctatcaaac gtgcctacat 180
ccccaacttt gaatccggcc g                                          201
```

<210> 4
<211> 241805
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241805)

<223> n = A,T,C or G, or insertion/deletion polymorphism (see Tables 1-2)

<400> 4

```
tgaagaaagt cattggtagc ttgatgggga tggcattgaa tctataaatt accttgggca 60
gtatggccat tttcacgata ttgattcttc ctacccatga gcatggaatg ttcttccatt 120
tgtttgtatc ctcttttatt tcattgagca gtggtttgta gttctccttg aagaggtcct 180
tcacatccct tgtaagttgc attcctaggt attttattct ctttgaagca attgtgaatg 240
ggagttcact catgatttgg ctctctgttt gtctgttatt gatgtatagg aatgcttgtg 300
atttttgcac attgattttg tatcctgaga ctttgctgac gttgcttatc agctcaagga 360
gattttgggc tgagacgatg gggttttcta aatatacaat catgtcatct gcaaacaggg 420
acaatttgac ttcctctttt cctaattgaa taccctttat ttctttctcc tgcctgattg 480
ccctggccag aacttccaac actatgttga ataggagtgg agagagagga cattctgtct 540
tgtgccagtt ttcaaaggga atgcttccag tttttgccca ttcagtatga tattggctgt 600
gggtttgtca taaatagctc ttattatttt gagatacatc ccatcaatac ctaatttatt 660
gagattgttt agcatgaagg gctgttgaat tttgtcgaag gccttttctg catctattga 720
gataatcatg tagtttttgt ctttggttct gtttatatgc tggattacat ttattgattt 780
gtgtatgttg aaccagtctt gcatcccagg gatgaagtcc acttgatcat ggtggataag 840
ctttttgatg tgctgctgga ttcagtttgc cagaatttta ttgaggattt ttgcatcaat 900
gttcatcagg gatattcgtc gaaaattctc tttttttttg ttgtgtctct gccaggtttt 960
ggtatcagga tgatgctggc ctcataaaat gagttaggga ggtttccctc tttttctatt 1020
gattggaata gtttcagaag gaatggtacc agctcctcct tgtacctctg gtagaatttg 1080
gctgtgaatc aatctggtcc tggacttttt ttggttggta ggctattaat tattgcctca 1140
atttcagagc ctgttattgg tctattcagg gattcaactt cttcctggtt tagtcttggg 1200
agggttacct acgtatctta atctcacctt caaggctgcg aaagcacgta gtacatgttc 1260
gaagaaccaa gtggaggcca gggtggctga actgtcaagt aaagtttgag atattgtcaa 1320
aggcccaatc atgcaagggt ttgtaggcta tgctaaaaat ttttcatttt attgtggaaa 1380
aatggaaaag tgattgaaag gttgtaatca ggcaagtgta tggttggcat aatgactaaa 1440
aaagattatt ctggttgcag agggagaaga attttgagaa ggccatggga acacaacaaa 1500
tgtgacaagt gctgggctga gggaagtaaa gagagttctg agggcatgca tatctgattt 1560
tccccataac atcctctaga gatacttttt tcccagtcca agatccaccc tagggtcatg 1620
cactgcatat ttctaaactg catatctcag cctttcttta tcttttatga ccttgccatt 1680
tttgaagtat acaaaatata ctgcaaatac tgtactttag tacttaaatg tcccttagtt 1740
tggacattct aaaaaatgag aaaacattgg tttgactgat gttttctcat gcttagattt 1800
ggggcatgca cagtaatacc acagaagtgc tgctgtgtcc ttcagagtgt gtcacaccag 1860
gaggaacatg atgtcagttt gcctcatatt agttttgatt gttgtgttga ctttgattcc 1920
ttggttcaat gtagagccta ttgtatttac cacatttcta gcttctataa atataatgcc 1980
ttaatatata taggggagag agagacaggt tctcactgga gtgcagtgat gtgatcatag 2040
ctcactgcag cctccaactc ctaggctcaa gcctcaagtg attctcctgc ctcaacctcc 2100
caatgtgctg ggattacagg cataaaccac tgtgctgggc ctaaacttca tgtttaacat 2160
ctgtcctgca tgcacatgcc atatacactt tgttctagat aatctgttaa tatgcctgac 2220
atattagtca tcttgctttg acctcctgct tgttttataa atacaaatta gtcagtccta 2280
aacctgctta ctctgccttg tctgttcctt taggtggaaa ccatagtaaa ggagcttgcc 2340
cacacttctc cccttgccct ctgcttccct gtgtggtccc ttgaggcaag atgtgtactc 2400
cttctcttgg gatctgtgaa tataacaaac tatattttca atggcagtta tcttttggtc 2460
tgttgacttt atcatattta aataataatg aaacatatta aaatatctga catatttttc 2520
tgcttaaagt cacttttttcc ctttttaatg aataagtaat ttgtggggag atactttaaa 2580
ctttttggc tgagatgcat atgagaaata tattttacat ggcgacacag tgtgtgtgtg 2640
tgtgtgtgtg tgtgtgtgtg tgtgtattgg tttgggctcc atcctgctga gtttgaggcc 2700
ttaggacatt ggattggagc tgttcagggg gcagttggct ctcaggagga aactcaggag 2760
gcactcagga ggamacacac acatcacaca cacacacaca cacacacaag aaacagtagt 2820
gttataaagt tatacatatc ttttccacat gaaagttatt ttggtttcta tgttgttata 2880
tttcatttga atataattct tgccttgacc tgctaaattg atttcattac cctctaaaaa 2940
gtaattacct ctgtttgcaa gcactagttt gatagaacta ccaagttgaa ttgtctggtt 3000
gccaaatgga aagtagatgg gaggggggcaa aactgatagc aaggagctca ttctaaggct 3060
ctccctataa tttagattga tgagtggatt gataaatttg agttaacaga atttcatgat 3120
tgattggcaa tgggggtgga aaaaagaagg agtcaagaat gatgtaaatt tcagcttggc 3180
ttctggggca atggtggtgc tgaagcttct tggtttcact ttcacctgtc tctttcggtt 3240
gactgctctg aaaagtccta tatacatata tggagagaga aatgtgaaaa ctaaagaaat 3300
tatctttttg cattatagag aaacactgct ggcttaaatt gcaactgaat taacctgggc 3360
tttcccagat actggtccat agatttaatc accccaatct agtaacaggc attctcaggt 3420
atggatgcca gagataaaca cgtgcatggt gcaggctgtt ttcaaacgtc acgaattggg 3480
gattgcattg agaaaatggg ttattctagt ggaaaagtgt gtgggtccac atacagagtg 3540
ctgcgaatga tgggctgtgc tccgctaggt ggtcccccat ccctacccct tttctgctct 3600
cctacctccc gttctccctc cctcctttcc cctcttctgc gttattctgg gattaacggc 3660
ggggtcggcc ccatacacaa acgcagctgg ctagtacggt cagcctgagc cctgctgtgc 3720
aaccacgtca ggaattccag taagttggca acactggagc acaaagacaa caacaattga 3780
ggaactcttc agtacagaaa ggaatgtttg gagccctggc tgctacagtg aaagggcaca 3840
```

cacacacaca cacacacaca cacacacaca cacacacaca cacacacaca cacacgctcg 3900
cgcctgcgcg cccacgggcg cactggaggg agcccagccc ctcccgcact cgcgctcctc 3960
cctcccgcca gccggcggcc gctctttgta agtcggaggt gcggggacgc tcattgacta 4020
tgcagcgcgg ccccagcggg cgtcggaccg gcttgacccc ggcgcggtct cgtaccatcg 4080
cctcggccgc ccggaaccgg cataaatcac ccgcgaagac tggagtgcag catcaagccc 4140
cctcgccgcc tccctcctcc cgctccggtc cggtcgcccc ctccctcccc agaccccagc 4200
tctcctgtcc ccagtcctgt ctcctccgcg ccgcacagcg cccaacacta tgcagggagg 4260
caaatagaga accagtgact ttggccagag cacagacctc tggatttccc aatccaggaa 4320
tctctcccac tctttcccac aacgctgccc gctccacctt tttttcttta agcctaagtt 4380
ttctcttttt gtgtctattt atctcttttt gtctttccga agtaacacct atcctttccc 4440
tcccctagcc cccacaccta aagctgcgcc taccactgca gcccacggaa gctacgcgat 4500
ccggactgtt ggggtcagca gagccccgga cgacctgtgc cccggggaaa ggggctggca 4560
gtaattggca ggttctcgcc cctggggaag ggaggcagcg ggaacctgtc cagcgaccac 4620
gtgcgttcag ggctgtctcc tccatgcgtc acggcccctt cgctggaggg aaagggctcc 4680
tgacttcttg gaccaggatc cggagcctgg gactagctgc cgcgctggtt caggggctgg 4740
agctggagat gatgggatgg cctcaggccc gcaaacagcc ccttctcaca cagggttccc 4800
accaccggga aataacttgc atcaaccctc ctttttttacc cctccctgtg ggctctgatg 4860
tcacgtacag gctgaggacg tgcgctgagg gcgggtgtaa ggccacttgt gcttttggct 4920
tccgggcccc ttgccagcct gtccaaagcg gccccaaaga agggaggcta ggggttccct 4980
gaacctctcg tgtttctccc tcttataaaa gggtaccgga accatggaga agacgttcgc 5040
tctttttcaa ttttgcttca aaatgagcag acttgtaaga agcacgatct ggccatgaca 5100
cctgtagatg tggtgctgaa taattgctaa ataaggatcc aacctcccca acaaagatcc 5160
acctccctct ctaatttgta aaaacacaaa gcaccccatc tcagcagcct gtatcctatc 5220
aggggaaacc aagatatccg aaggagccta gagagatcag gccaggaatg aaggtcacag 5280
atctccatcc agcaggctct ttactccttc ccttccctac ccccgcctct ttccctttct 5340
ttctctttcc ttcatttta cttgtctggt tgtgctttcc ttttccattt cttatttttt 5400
ctttctcttc tctattcttg actttcctcc tcgtccattt ctttccattg ctcatttagt 5460
aaaactgcgt ccgtgcagat ttccccgtga gccgcctcgc cggcttctgt gcggggcaaa 5520
ccctgcggag aggcgagggc agcgcgtgtg cacgtgtgag tgtgcctgtg agagtgtgcg 5580
cacaggagtg tgctcttgta tgcacgcgta aaggggactg tgtatgtcgg cgttgaagtg 5640
tgactgtgga atgtgcgcgc gtgtgtgact ggcgtgtatg agtgaatctg tgtcagttgg 5700
tgtgacactt aggagtgcat gcgcctgtat gagtgcgtgt gtgagtgtgc acacgcctgt 5760
gtgagtgtcc ctgtgtgagc acgcgtgtgt tcgagtgccc actcctcccc gcgctgcaaa 5820
gtgcaggggg cgggccgggc ggcagggggc ctgcccgctg gattcccgca tgcttgttcc 5880
ggggcggtcg ggtctaaagg gctttatgca ctgtctggag ggtggggact ggcgcgggta 5940
gaaaacggga tgcctcgggc gtgggggcag gcttttggcc actaggagct ggcggaggtg 6000
cagacctaaa ggagcgttcg ctagcagagg cgctgccggt gcggtgtgct acgcgcgccc 6060
acctcccggg gaaggaacgg cgaggccggg gaccgtcgcg gagatggatc gcgggccggc 6120
agcagtggcg tgcacgctgc tcctggctct cgtcgcctgc ctagcsccgg ccagtggcca 6180
aggtaagarc ccagccrgag cctctcgtgg agcccccact tccccggctg tggcagggtc 6240
gggtccgcgg gaggccggag gggagagcgt ccgggcaggg gctagggccg ggcggcggcg 6300
cgggagctgc tcccggtggg gcgctcaggt tgcttcgcga agccggagsg ggmgcgcccc 6360
tcttcgctcr ccaggaactg agcggcagca aacttgagaa agcagccccg ccagtttcgg 6420
tgacagcgca ccccacggag accctgtctt tgttcccacg ggcgttggtc cgatgctcct 6480
rgaaagcact ttgcgggaga acgaggttct ccgccgtttg cagcctgccc tccctagcgg 6540
agttctctgc tgggcggcgc ggtcccgggc tctgctcaga gcgcagcttt ccacctgcag 6600
cgcccctccc gggatccctt cgcgcgccca gggccgcggg ccagagcact cctcccacca 6660
ccggcgaaac ttggtcccgc ggtgaccccc agagaccgct ctcaccatac agatcattta 6720
cgagccaaga taaggccggg aggtgggatt ggccgagaga gtggctgagg gactggagtc 6780
ttttcttgaa gttttccttt ccagctggga gctgggggct tttgtgttga tgaatggggc 6840
ccgtctgcat ggccagagtt ttggggatcg aatgcagaaa gtttctagta tgaagtgctt 6900
taaacttctc tcaagttgtc cgatagttta tgttttaaca gaaacagaga agagggaaag 6960
agagggagaa agaagcggag agaataaaac tagtaagaag ggaagaggag agagcgtaag 7020
agaagcaaat aggaataagg aaagaaggag ggaagagaac gactggggcg ggagaagaga 7080
gagagagagg acagagagga gagagacaga gagagagaga gagagagaga gagagagaga 7140
gagagagaga cagagagaga cagagagaga cagagagaga cagagagaca gagacccggc 7200
cgaggatgaa tgggaagggc gaggaggagg ctggaaccgg cgagctctcc ccctggcttt 7260
gcgttgctag gtagcagccg ggagctgcgt gtgaccgacc accagacaga cagaggggac 7320
gctgctgcca ccgcagggac taatctgtct gtggggatgg gagagtcccc cctttccct 7380
cctgctcctt ccctcccgtc ggacaactta attgccctac aatgaaaatg aaacccctat 7440
tgttgtagga ttagccaaag caataaattg attttcctgg atcacatatt ggggttgatg 7500
ggtggggaat gtggaagccc ccatttacgg aggagtgagg ggagggcttg tggatgggcc 7560
gtggcatgta ttcaaatggt taatctgctt tctttcctca attcttagcg taagctcctt 7620
agagggaatc aagtaagtaa ttatacagca actcctagca gcacccattt cagacttcct 7680
gggaagaagt ttggaaaccc taacaaaccc cacaggtctt gcaaaagtct tcagaaaggc 7740

aggagaggca aggagagatc attaataacc ttcctttgaa cacccttct cagtgttggt 7800
aacgcagaaa gagggtttat tattattgtg cagagtttgc acaatgctta gggttgtatc 7860
tcatgtccta aatatagcta taggatttac tatatgttcc tgtcagtgcc tggcaaaagg 7920
aaatcttacc ttgattcatc tatgtccttg tacaaccaaa acagatattc tttttcctgg 7980
gttgatgatt tagtcactaa ataaccaata cctactcttc ttgatagttt tttgcaccca 8040
tccatcttcc attctatgat aataatatat aataataatg tgtatagtaa tagtaaccta 8100
gcatacacat atatgtggca ggctttgttc taagcacttt atrcttattg actcaattaa 8160
tcttcataat atcccttgga agtaagtact cttattatca ctgttttaca gatgagaaag 8220
tggaggcaca gaacaattca gtaatttgtc tcagttcata ctgctagaaa atggcaaact 8280
caagggattc tgaattcaga gtctataatt gctacagtat acagtgtctg gttttctctc 8340
tctctctctc ttttttttt ttttttttt tttgagagag acagaatctc gctctgtcac 8400
ccaggctgga gtgcagtggt gcaatctcgg ctcactgcaa cctctgcctc ccaggttcaa 8460
gcgatcctca cacctcagcc tcccaagtag ctgggactac aagcccgggg caccatgccc 8520
agctaatatt ttgtattttt agtagaggca gggttttgct atgttggcca ggccagtctt 8580
gaactcctga cctcaagtga tctgcccgcc taggcctccc aaagtgctag gattacaggt 8640
gtgagccact gcacctggcc cgatttctct tttttctttt gtacaaaaaa tgtcatgctc 8700
cctaacttac tgtccatgtt tgaggttccc aaagaagctg agggrcaata tgcaactcgt 8760
accacctgct gcttcataac tgtggatctt tttccagaat ctctcctcag gtttctaaga 8820
ccagaaccca agtctcccca ttcccagtct tcctacttga tcattttaag acgcatttcc 8880
tctgaatgtc ctctgcctga tacgttgaga tttctagaat cctgttgtaa tgatcctgac 8940
ttaatatatg aagtaaaatc caatgagatt gtaacagcct ttatttaagc actacctttt 9000
aggtaggcta ccattgcaaa cttcgcatca ctaaaaattg gaggggaaaa aaaagagctc 9060
tgagtattct atgtttagtc tttgaaaaaa attataccac atctgttgtt aaaaattatt 9120
tgcattttcc ttatcttttg tgtaatgctt ttcaagaaaa aacattttgc agagtctgaa 9180
ctcgagtcaa gctgttgggt tccaacattg gctttaccac tttctagctg tgtgaccttg 9240
ggaaagtcaa ccaactttgc atagctcaga tggcttatct gcaaaattga caagataata 9300
agagaattta cccaatgaca tcttgtaagc ataaagagat aaaatatgcc aagtgcttag 9360
catggtgtaa agcatataga cagtgaaaat aaactagaaa ataatctaaa aatayaatat 9420
ttttattata tttatcaacc cttaaagtaa catattgttt tgcttcctat tcctatttcc 9480
atttccaatt ttcaaatata caaaggaaag tcttctttaa gcatttttca ctaacagttc 9540
tctgaagact tctcagaccc tagcatgtga ttggaagatt ttttcytttt ttttttttt 9600
tttgagaaaa tcgtattggc cttaaacaaa gttgtattct gtttactaat taaaaaaact 9660
tatttttcaa aaatagaaat ggggtctcac tgtgttgccc aggctggtct tgaactcttg 9720
gcctcaaatg atcctcctac ctctgcttcc caaagtgctg acattayagg caggagccac 9780
cttacctggt ccaacattat attctttaat ccaataaaaa tgtggtaatg tttttaagag 9840
ttagtatcag cttttatgac aattacatct tcacatgaag tttatatgtt taaaaggatt 9900
gtgggggcaa tagcaaactt gtatcgtttt tattccatca caactctgga acctcactgc 9960
tgctttaatt tcacagttgt tggcttctct ttctctactt gaaaaagttt ctctttacca 10020
gtcttcataa gacttctgcc tgaactccct tcagtcatgc acctgtctca ttttaataga 10080
aactcagact ttttacagct agagggaacc ttagatatca actggtctgc ttgcattttt 10140
tttttcttac agataagcaa ttagcccagg agggagaaga aaggggctga gaggatgaaa 10200
gggaaggcgg ttaataggtt tcttgcctaa ggacatctag cctgtgayag agctaagata 10260
taaatttgca gtggaccatt ttttagattc atgccttctg aatgtcccca gcctgtttgg 10320
ttggttgaga tttctagatt ccttttggaa tcctgacttg ccagataagg cacagtctga 10380
taagcagatg aatcttaaaa acaattggat gggttacctg tccctggcca aagaggaatc 10440
ctgtgatagg ttattacaac catgtaccat gcgctttcag cttggtccag aactgatgcc 10500
atgtcagtgc ccctactccc aaagaccata cctccagatc cattttcaa attcttgagc 10560
catcaaagyg cattcctgaa gatctttggg ttttgtagtg caggctgctg taagactagg 10620
ttttcagtct tactaaaggt aattattagg tcataatcat tgttcatgtt ctctagtcag 10680
gcactgtaag aacactgaaa ggtttttaaa atatttaaat taaaatttta aattatcatt 10740
taaaaataat gataccagga acctagatgt atttcctgtg taatcagaag caagtgcatt 10800
gtcatattgg ctttggagtt tctgttaagt cctagtagct agaacaaggt aagtagaaag 10860
tagaaggtgc tgagctgggc gtgggggctc atgcctgtaa tcccagcact ttgggatgct 10920
gaggcgggag gatcatgagg tcaggagatc gagacctgcc tggccaacat ggtgaaaccc 10980
tgtttctatt taaaacacaa aaattagctg ggcgtggtga cgcacacctg taatcccagc 11040
tactcgggag gctgaggcag gagaactgct tgaacacagg aggcagggat tgcagtgagc 11100
tgagattgtg ccactgcact ccagcctggg tgacagagca agaatctgtc tcaaaaataa 11160
aataaaataa aataaaataa aataaaataa aataaaataa aataaaataa aaataaataa 11220
aaaagaaaaa aaaaagaaaa gaaagtagaa ggtgcttatg aaagagtgtt gaatggatag 11280
gaaaggggtt ctcaaggttg actgcacgaa tctagagcaa ctaaaaaaat actaattgtg 11340
aagccctatt ctagcatgga aaaaataagc ttgatggaac ctttggtata aatcaaatgg 11400
ttctatcgta tcctattaac tttatagtct tgagtaatta aaaattttta ccactattgt 11460
gtattctgtg aatgtttatt ttatttttc catgaatatt tattaaatat caacagtgtg 11520
ctgatgagtc aatagtatca atactacaga aacattaagg aagatgagaa ctgaaaagag 11580
gtgtctacat atctcgcaat taaaatggac tgcagttttg catttaagat tctgaaatag 11640

tcattgactc attcctaata accctgccca ggatctcacc agcattagaa agaytggaga 11700
tgtttcagca tccgagttct gggatgcttc ttgataatga tcagctagta gttgttttga 11760
aatgtcaaga gcatttctgt ggttcttcac atgttcctaa tgcaaatgtt tccgaagtaa 11820
tttcttgaca gttacagtgt tttgagatga agtgggaagg gcttgtgatt ttraagttgg 11880
aggatcttgg tttgattcct acctctgcca tttattatct gggaaatcca gtaccacaca 11940
tgctgggtgc tctggggcag ttttcttatc tgtaaaatgg acatatatct acctcacggg 12000
gtggttatgc aaaggcaatg aatgtgaaat gtttaataaa ctgtgaagtc tcatatagat 12060
ttccattcat cattattacc caatacgaga attttacttt ttccaaactt gagaggagga 12120
agatgttgca gtattttggt atcttcttta ccgtgggtct gagaatgatg cacctgtgca 12180
tgttgttaca tccttacagt ggctaccaca acttcacatg ttattcagta ctgttatgtt 12240
ggtgaatgtc acaaaactaa gttaaactgt ctgaggcaaa aaaggaaggt tattgaaata 12300
catagttgag gctgggtgtg gtggctcatg cctataaatc tcagcacttt gggagtctga 12360
ggtgagcgga ttgcttgagc ctaggagttt gagaccagcc tgggcaacay agtgagactc 12420
catctctaca aaaaatacaa aaaattagcc aggaatggtg gwgtgcccct gtggtcccag 12480
ctacttggga ggctgaggtg agatgatcgc ttgagcccag gaggtcgagg ctacagtgag 12540
ctgtgatcay gccactgcac tccagcctca gcgacagagt gagaccctgt ctcaaagaaa 12600
ataaatacat agttgaaaag atacagataa ttaggttgat ccatttgaga ttgatttttt 12660
ttcctatgca gaaatagtca aatattggca atttcatttg gttcaaccta atataaaatg 12720
gaggctcaaa ctatgtcagg ccaatcttgt ctttttccg tctcctggct ctgagatgac 12780
tccattctta aacatgttct cctttgatgt aaagcggctg tcagtggctc tggagccacc 12840
tcctatcaga tcacatccac tgggaaagaa aaagagtttt tatcttagct attcccagca 12900
aaagtttcag ttgcatctca gggtctctac ttaggtcata aactcattgg agaaccaacc 12960
actgaatccc gggtcatgat gtgttcccat ggcttaggct tgggctgtat actcagtctt 13020
tgagatcatg tatgaagggg tggagtccag agagaaatgg gggtaattat tgggagaatg 13080
gtgaacagag gctgggatgc aaaaataaca ggtgttcagt ataccttatc agataaaatt 13140
gactgacgat gttattttca ttttgtatgt gaagacacac ttgaaaaagc tacagaaatt 13200
tctcaagagc tggcagccct ggggtaactt acagaattga aaggaataaa gtattggaaa 13260
cattaagaaa aaagacatgg tgatctgtgc ccatgtgacc atgttgcaac tttaagttta 13320
gaaggagaac aggagaaaga aggactttta gaaggtttat ttggatccta aagttttctt 13380
atttggagca gagctttgtg atagacagga aagttctgga aaatgagctg agcgatcaga 13440
ctacaggatc ccttaagtcy kgtgcagtat ttcatttttc tgtgaatctt aggctcctac 13500
tccttttcca atttacttca ctccaatgtt tatgttccta agagtttgtc tgttttccaa 13560
gcactagtcc tttgctataa ggatggggta gagagaaaga agcttaaaga gtttgcagac 13620
aggttaagat gcttytgtgg agacagaaca catcttggtg cacatctgag tgtccttagc 13680
acttcatcta tggacttctt tcataaatgg tagaacacgt atccatcaca ccttattgga 13740
ttaattcaga aatgccagat atatgtactc tttgctgatg gttactttkt tggtctctaa 13800
tttaagtctt atctctaatc acattagctg agaaaatgga gacattatca ttctaaaaat 13860
aagatggtta acttttatat taggacactt ctgatttagg atagcactga aattcagtgc 13920
aaagaaatgt aagtctttcc tagataatga cagattagac aatttgaagt ttcacttttg 13980
gtcattagcc ctcaggtcat gcctgacctc aaggttactg gaaacagtga gaaatgaatg 14040
aaaggaggaa atgtaattac cattctgtgc attgaatagt tgagccactg ttaccatgga 14100
tacaatggcg catttattgt ccagatcttg agatccaagt ttgtaagcaa tatccaaggt 14160
ctcctttaaa tttatgtact atcagcgaat aacacatgaa gattcctggt aactttgaaa 14220
ataagtcttt cctcactgat ctactgattc acattaagta agagcatgtg tacttttgaa 14280
ggtgttgagg aaacctgaaa aagacgaaaa ggaaagtagc tacacttctg ttatgctgga 14340
cattcttgga ttcctctata aaaatattct gtcttatact gtcagtgatt tgcttgtcac 14400
tttgggccca gttctttggt ttttatgtca ttaacaagga gaaaatttcc tgagtaaagg 14460
ttgaaaaaat caaaatcgtt tatttttatt ttttgagaca aggtcttact ttatcaccca 14520
ggccagagag ggtctcactt tatcactcag gctggagtgc atggctccct gcagcctcaa 14580
cttcccaggc tgaagagatc ctctccgctt aaccccacaa gaagctggga ctacagacac 14640
ataccascac tcacagttaa tttttatatt ttttgtagag atgaggtttc tccatgttgt 14700
tcaggctggc ctcaaacccc tgagctcaag tgatcctccc gcctcagctt cccaaagtgc 14760
tgggattata ggcgctagcc accatgcccg gctgaaatca tttattttgt caggaaattc 14820
ttaaagttga atttaagaat gaaagtattt tatcagaaat atggcaatcc tacccacatt 14880
ttaatctcac tagaaggggg gtgatacatg ctagcaagta ctcccacact grtttaattt 14940
tgatgtgagg aagggtgtgg agaatacttt ttgttgcaag aaacagaaaa cccaactcaa 15000
aatggcctac acaataaagg gtatttcttg gcttatgtga gtaaaaaata ctgaggcaga 15060
gtggggttca ggcgaggtgc agtcagggct ccagttctct ttctttgtgt tttccttgac 15120
cctactcccc cctaagtttc acctttgtgt gcggtctggc ttcccatatg attctratat 15180
ggctgccagg gcaaatgggg ctacgtgttt ccttgatcct atccaggggg aatccaactt 15240
tgagaaggtt ttagttatgt tctcaaaagt attatttcat cacaataact tacagattgt 15300
tagaatttct aaggacccta gacaaagtca gctagctccc caaacttgrc atatcatcaa 15360
aatcacctga ggaacttaaa aaagtataga gattcttaaa tcaaaactca cccttactaa 15420
agcaggggta tgaaaatctg tgtkttttaa aaattttatt ttattttact ttcagttctg 15480
ggatacatat gcagaatgtg caggtttgtt acataggtat acatgtgcca tggtggtttg 15540

ctgtacctat caacctttca tctaggtttt aaggctcaca tgcattaggt atttgtccta 15600
atgctctccc ttcccttggc ccccaccccc tgacaggccc cggtgtgtga tgttcccctc 15660
tctgtgtgtg atgttccccc cccgtgacca tgtgttctca ttgttcatct cccacttatg 15720
agtgagaaca tgcggtgttt ggttttctgt tcctatgtta gtttgctgag aatgatggct 15780
tccagcgtca ttcatgtccc tgcaaatgac atgaactcat tccttttttat ggctgcatat 15840
tattccatgg tgcatatgtg ccacaaccaa cccaaatgcc catcagtgat agactagata 15900
aagaaaatgt ggaaaatctg tatttttaaa agtttcaagg tgattctgag ggctggacca 15960
atttttggga acgtgtgatc taggtaccct ctcatttttc agttttgtaa acagacttag 16020
aggtgaactg acttamcact gcaaatttct tcagtggcag ttaaatatac tctgttaaat 16080
ctctttcttt tggatgggaa tgttacaagc tagctacaac aagaaggaca ggactctttt 16140
aagtctgagg gtgacatgaa gtactaccct cattcctggc cacctccttt tttggccagc 16200
rtggcaggtc ctgaacctct ccctaaatat gccactgttt gtgtcttaat tgtatgtttt 16260
gttcttacct tggtcacctt tgaagttccc cccagaccct cctaagaacg ttggattcat 16320
tgaggtaaat aactgttgca ggccttctaa tcttttctca cctgaatctg aattcatctc 16380
agaacacccc tgacacagcc cactggcttc tagagaagct gtctgttcca tgcttggaat 16440
ggaagtattg aaaaacttca tggctcattt cctttgtatc ccagcctcaa ctctttgttg 16500
acctcattgg gacttacagt ttgttgatcc taccgcctct tcaccatccc tcaaatccct 16560
cacctattta cttcctcagc ttatatttta tggccatcat taatttcact tccctgcata 16620
catacrcgct cagcagcttg gccccctttat ctggctctgt tgtgcttggc aaggccctga 16680
tcctggttaa atccagttct ccacatctgc aactctgtag ctaaacatgg caggagaaaa 16740
acacaactat actgactagc ctcgcttgac attcatgaag ccaatctcaa gcttargact 16800
tgcttcctag tctgtctatt gcctctcttg cttccttata tcttctcctc tttcctcaaa 16860
cctctgacat caccttctca catgtagagt gagcttttta aaactgtgaa aatggaagca 16920
accagaarag aattccataa acttctataa ctcaaccatc atcatttgaa cttcgkctta 16980
tatcttctgt ctttcctcct attactctgg aagaattttc ccagttctta agtccaacca 17040
tttcattcat gttctagatc tcattccctc tcacctctct gcaattgtcc cctctttctt 17100
ttatgaaatc ctctrttcca cattaccttc taactatcac tctatttttt cggttccact 17160
ttacagtaaa attcttgtac agatgtgcct atatccactg taattacctt tcaatttttt 17220
ctcaaatcca tgccattttg ctttagccct catccttgat agatattttt ttggtcaaag 17280
tcactcatga sttccatgtt gttaaatcca atgatctatt ttcagctctg gtccttattt 17340
aactggttag cagcatcaca cacagtgtat ccwgacttcc tccttgaaac acttagttag 17400
attttcaaga aactgccttc tcctggtttc ttttcttcct tgctggccta cccttggtat 17460
ctcatgcttg ttcctgtcta tatccctgac ctgttttcat ctctagctac actgcctcct 17520
tggtggcctc atcctgtctc atggccctct ttgaagcagg gagtggtttc ccaattcagg 17580
gaggcggcat ggactckggt ggaaagaaca tcacatgtca agtcaggaca ttcatggatc 17640
ttgttcctga agaaagaagg aaaaataggc acaaccaaag agggccccag gctgctgaaa 17700
aggacccagg gccacttgtc ctctggggat agtctctgtc atctgagtcc ccacttttt 17760
ttttttttt ttttttgcg atggagtctc gctctgtcac ccaggctgga gtgcagaggc 17820
gtgatcttgg ctcactgcaa cctctgcctc ccaggttcaa gcgattctcc tgcctcagcc 17880
tcccaagtaa actgggatta caggtgcaca ccaccatgcc tggctaattt ttgtattttt 17940
gtagagatgg ggttttgcca tgctggtcag gctggtctca aactcctgac ctcaagtcat 18000
cctcctccct cggcctctca aattacaggc atgaaccact gtgcctggcc tcagtcccca 18060
tacttttgag gactccatat atacttcttt accatgtaca tgctgacaac tttcaaattt 18120
atgaatctaa tccagaccac taccctatag tctagaccca catatccaac tgctcatttg 18180
acatgtccac ctggctggcc aatagtcatc tcagacttca catgtctgaa attgaactcc 18240
tgatctccac taatgtccaa acttgctttc catgtggaat ttctcatctc agcaaatggc 18300
ttcctcatcc ttgctcaagc ctcaaactgt atcctacttt gacttttctt ttgctcctct 18360
accccatata gaattcctta gaaaatccca ttgttttgat cttcaaaata catctagaat 18420
ccaactactt ttcaccatct tcacttctgc caccctgatt caaccractg ccctctcttg 18480
cctcgacgat tgcaatggct tccatactga tttccttgct gtagcaactt ttttagaaca 18540
tcagtcagat cacagcaccc ctctgctcag aagctcccat ggtttctgtc atactcaagt 18600
tgggttgccc aaaaacagac actgagatgg agcttggagt atataatatt tattaagatc 18660
aatgcgtgtg aagggaaagg gaggaagcag gatgggcaga agaagaagtt gaactctggc 18720
agctgttggt caacccagag gaagctctgg agcaagagtt gcctgttaga gtgtcctatg 18780
tcaggctgaa atggccttgc ttaatcactg gatgtggcct gtcctggaag gacacgacct 18840
tgggcaggtg gctttctata gctgaggcag accccaaagg agctgattgc aggaagaaag 18900
tccttcctca tagctggtcc ttcctataag gggaagctgc atggcacawc tctgggtgta 18960
ccactgcttc ccatctcatg aagagtcaaa gtccaagtcc ttactatgat ctacaagacc 19020
ctaaccattt ggccttcaca tcacctccct gacctcattt ccttctcctc tccccatgca 19080
cagtgcacca ggcacagtga tatccttgtt ttccctgaca tggtgagcac ttttgggcct 19140
ttgcacttgc ccccctttt cctaaatgct cttgcctcag atggtgcatg acttacttcc 19200
tttcctccta caggtctttg ctcataggtc accctctcag tgtggccttc tctgattctt 19260
tcccgacctc ttctttcctg atttactttc tccattgcgc ttaccaccat ctgacataag 19320
gtatgtaact tagttagttg tttgtttatt tccttactta ttatcttccc ttccctaaga 19380
tgtaaatggc acaagggcag ggattttcat ctcttttatc cattgctttc cctagtgtcc 19440

agaaaagggc taaataaatg aatatacatt gaataaatga atggacagat gtcaccatgg 19500
gtgctaagaa ggggcatcct cagctcatca ccattccctg gtactaccag cccttaattc 19560
ctcgaggccc ctggaggccc agtcarggtc ctgatggaga aaaaggaaaa ttgctgtctc 19620
tatcaaagca agtggcttag caacgctgtt tctctcgatc tgactccccc cttttctcca 19680
ccccagtgcc tcccactccc gccctgctgg tgattcccaa tgcatttgag tagttgaatc 19740
tgcatccttc tttttaactt ccatcccaga tacttggtta ccctgtgaga attcccctgt 19800
acatacagaa tgggtcattc tgctattttt aggacagatt tgatacagta gcttttacaa 19860
aaagataagc caaagttttt agacwtcrtg ttagtggact gtcattctgt atttaaacag 19920
aacacaaaag aaagctgtct gagaccatga cacagtgaaa acagccttga tcaaacaaaa 19980
ggccctcttt gaagagggga gtggtttctc cactcaggga ggcagcatgg attgtggtgg 20040
aaagaacatc acatgtcaak tcaggacatt catgggtctt gttcctgatg aatgaaggaa 20100
aaatgggcac agacgaagag ggcccctgac tgctgaaaag gacccatggc cacttgtctc 20160
ctggrcatag tctccctcat ctcagtcccc attcttttga ggactccata mgtaacaaat 20220
aggttggagg caggagartg atggaattcc acacatagat gagtagagaa gttgggaaat 20280
aagccacaat aaaagtgact aaattatttg agtgctttct ataccaggca ttggcctaag 20340
tgttttgtag gtattagttt acctacttay gtagtaacag taaaaatttt atggataaag 20400
gaccaagaca atgacaggtg aggtaatttg cccaaagcaa ttcagttact aagtggcaga 20460
gccaacattt gaacccagaa cccttatttg tatatgttgt caccatggat aatttggagc 20520
aagtggaaga tagtcctctg tacgtaatca aatgaagcct catttaattt ctcatattat 20580
gatcagatga cctcatttca gaggctggta ccattgcgac ccaacttttg gacatttttt 20640
tgctactctt ggcagttcat tcattcattc attcattcaa tatatgttgc agccttatca 20700
tgctctaggc gtgatgtaac taggtactgc agagtataga cagagacctt caacataggc 20760
cacatccaaa acaacttact attgaacaga gtatatttcc acttccttct agaagactag 20820
aagactgtac tttttaggta cggattgatt tctctctgct gggtttctcc tatattacta 20880
tttcattatc tgggaacacc tttttttttt ttccctctat aattatgtgt cttttaattc 20940
aaaggaccct tacctaatca gagagttcaa ttttaacctt ccgttaggga cagcagtcat 21000
ctataaattt tcagaggttg ttgttgttta ctactaatga aaaaaattat taagttctct 21060
tatttaaagt cactgaagaa aaaaatgaac aaccaagtga gagctgagtt tctttacttc 21120
ccggagaaca ctgctgttgt agagatggag ragacatttc ctatgtgctg gatgtgctta 21180
aaggtctctt ggtcccaaag tatctctcac tacggccaaa gatctctgct ctgtcattac 21240
taaagtcagt tcttcggagt aagacattct ttcctcctga aactcctatt acaatgtgga 21300
aatgttcact cctgtagggt aaagtagtta gttgagatag taatgcacag taaatgtttg 21360
tcagagcaag gttcagagag aaggagacac aaagctggta tgttttaatg gggatgaaag 21420
agggaaagaa ggtactagag gtgtgatata gtcttgaaaa taagccaact tccttttctg 21480
gggaataaag ggttattatg cttgtgcttt ttcttagaat ggctttatgg ggaatttcag 21540
ctgtgrtcta ttaggaaggc ctcaaagata gaacttaaaa gcttctagta tggctgtcct 21600
tcctctagtt agcaattgaa actgagttgt tacaacaaaa ggaaaagttg tcgttaaaag 21660
caacacagtt gcaagactcc atcaaccatt ccttggggat tcatcagtgc ctggtaagtt 21720
tgagaagaga cccttggatt ttaatatata tggcagttat aatttgtcta gaccataatg 21780
attactatta atagggaatc ctgtttttct atttttaaaa aaatttagag atgggggtct 21840
cactatgttg cccaggctgg attcaaactc ctaggctcaa gtaaccctcc tgcctcagcc 21900
tcctgartag ctgggactaa ggtgtgtgcc actgtgccta gctctgtttt tctttaaagt 21960
tactgtgtaa taaaaaaaga atttgcaaat gcataaaatt gaatatacac atgtcccaag 22020
tcaattgtca aatgattggt ttttatgtac caaaattctg catttttttt tcaaggtcac 22080
ttctgatata agaatttact tcttccctaa tatttggttc agtgaagtgt tgaaagaatt 22140
tgctaagtaa tcattgaaag ctaagattct agtgaaamac aaaatgcatg gtttaaaaat 22200
tgaacrtact aactgaaaga cagtggaagt tagatgcttc ttgctgtaaa taattaaacc 22260
caacagtgca gacgagagaa catggcacca agagggactt gggctaagaa ggatcatatt 22320
gtattgaaca ctttcgtttc cctgtaaggg aaatcaaaag ggtctttaat agttgttgct 22380
gattgtgaat atgtgcaaca aaatcccact gtaatccaga tttatttttc aagcattttg 22440
ctgtgattga aggaaggaga aagggatagg aagaggatgg agttttatta aagctgtagt 22500
tacttcttcc ctttaggagg tctaagtgtg acttgtcaca gtgacctggg actttgattc 22560
cctccagggc cttcctgttc tatgggcaca ttggtggatc aaagacaatt gacttttgtt 22620
ttgttttgtt ttgttttgtt tttggagaga agcagtggtt ctgctaactc agaacaagaa 22680
cgacaagagt catgtaggat gtttttctga gtttctctaa cagtgctcgt ttttttttt 22740
ttttttgacc gccccctctt ttccttttga ggtggggcca aggggtcaaa cctccatttt 22800
tctatctgta aaaaagagaa tcggccttta tgaagtgctt taattttaaa aattaacata 22860
ggctaaaatt gctgtgtgtg tgcacagttc tgtaaatgtt agtgcatgta tatatttgtg 22920
tagccacaac ctcattcggg attagaacag ttcaatcacc cccactaact cccttgtgct 22980
actcctttgt ggccacaccc tcccaataaa gtgtgtttta agttcctttt ttgaaaactg 23040
accttcccag atgaatgtct ctgttgcctt ttatttgttc atttttattt acgcagtgtt 23100
ccttgctcat ttttgaagta attcaaaatg acactcacgg taagcttgca agrctgcctt 23160
tcctttayta taacggagaa aaaattctgg aaagaaggca gctctttcag tatagtcata 23220
taagaacaaa atttccccaa acttggcttg tggctagatt ggaatccgta aagaaaacac 23280
actcaagaaa tctctcttga agaggaggac agaggtttat tttttattta acgatttacc 23340

ccttgacacc tgggaaatga ttagttgatg ttttcaaaga agattaagtc agtgtggtta 23400
attaactgtg gtaatcaggt gacttaaatc aattaactcc ttgttaacaa tttccatcaa 23460
ttttgtaaat aaatgactaa atcagtaaat tgtactctta agattaaagg ctattttctg 23520
atttatttt ttgatgacaa attagagtgt ttccttctca tctcagtcac tscctgccac 23580
tcttgctctt aatcataagc cagttttagt ttgagaggag cacaccaggg aaacttttaa 23640
tatatggttt taaggaaaag tcaggcttaa ggacaccttt gctccttcat ctcagcacat 23700
ttggaaagaa tgatttagtg agagcagtag ttgggggtgg gtgtagaaag caatcctgaa 23760
acacactcta ggataagctt ttattattaa gtcacttaat gtcttgtttt atttatgttt 23820
tctaagttaa aactcgatga gggatataat aaaatgaaac agggtttggc tcttagctaa 23880
aaataaactt taatggatgt cttacatgct ctatttagag ggaatttcac aaaatattgg 23940
gatatattga ctgcattcat ttgtaaagct tgattgcatt aaaaatacca tacaaatata 24000
caactaaaat gttgttactt tttagaatct ttataattga aaattctctt ccctgcttac 24060
ataactttat tatgtctttg tctccaatga aatatgagct ggataaacta acacaagaac 24120
agaaaaccaa acatcacagg ttctcactca taagtgggag ttgaacaatg agaacacatg 24180
gacacaggga ggggagcatc acacactggg gcctgctggg ggttgggggg ctaggggagg 24240
gatagcatta ggagaaatac ctagtgtaga tgacgggttg atgggtgcag caaaccacca 24300
tggcatgtgc atgcttatgt aacaaacctg cacgttctgc acatgtaccc cagaacttaa 24360
agtataataa taataaaaaa agaaagaaat atgagctgga aaattataaa accatatcct 24420
atgcccctga atatgccatt gcattctctg aggattttca ctgtaggaca gatgatatag 24480
gtttatttat ggtttcttca agaagggata tttggcatct tgaataactt ttgaggagtt 24540
agtaaatatt tatgtatttg caaaaattct atgctattct cacattttat aaagagaaaa 24600
tttctatggc ttcctttaag gtattaagga tagattaaat tgtgaaactg agctgaagcc 24660
actgttgtaa atttaaatca ctggctgcca agcaaaattc tgggctcttc ctattattat 24720
agaagctttc tggccatacc ccaactaccc cttcccaact tccctggaca tagttaacct 24780
gtggccaaac cctttctggt actgggacat ggtctggaat cacagctcag agatttagct 24840
cgactgcttt ccagatgtgt acctctgaag ctctctgagc ttcagtttcc tggactatac 24900
aatgggtgtt agtaatttct accttatagg tacctgggaa tatttaaagg atattgtgaa 24960
catgcaaggt cctggcactt ggtgagcatt cagtaaacat ttggccccac agggaacctg 25020
atattaaatc attcatagtt gaccagctct tggttaggtc atgcagcaaa gcagccacca 25080
tgctgtgatt ttttgaaata aagaaaccac ttgtcaaatt ctctatccat agaaattgct 25140
ggggaaaaat acagcttttt aaagcagatg aaactactag acaaaaaaat gttggaagac 25200
aggcctggtc acctgccttt cttcccccaa gaatgtttgg ttcttcacct cccaggtctt 25260
gaaggcacag atccaaatgt aaagttgcca agaagttcaa acgttggtgg acctggtgtt 25320
tccatttag gtgtcctgtg catgctttct gtaacttggt tttatgcaga acttgctgat 25380
gatgtctctg taactctgag aacaggaatg atggaagcat gggtctgagt ggaggtcaga 25440
tgtgtcctct gggcaaggag aaggatttgc ccagggaaga ctacacttga agaggagcac 25500
ttgattttgt gagaggtttt agacagagca tgtaagaatc acagtcaatg aagagtttc 25560
tctcttgcaa aagttcctta ttatttcatg aaactacaga aaggtcagtg agatgttcaa 25620
taggtgagaa agctgtcaag ctagacttgg ttaataatta cagttaaaat aatcactgat 25680
gtatttcttt cacrcacgtt tattgcaagc tttttttta tcaggaactg acatgcatag 25740
atgaataaga catgcaaata aacaattgtg ctacagggtg agaggtctat aatagaagtt 25800
tgggagcaca gaaaaggcag tgatgtagtc aactagacct gagaggacca agggccaagg 25860
aagaccgcac agattgccat ttgaactgag tcttgaagga gttgggagag tggactgtgg 25920
aggattttgt atgtcaagct aagaagtttg gtgcctttga agaaatgtaa gctgggaagt 25980
acaatgctca gattttcatt ttgtaaaaag aatacttgct gcaatgagag aaagcagatg 26040
aactagttaa gttagaggat tactgggatt atctgggtga cagatgatga gggtagaact 26100
agacttgtgc acttggaagt gatgagaaaa ggagagagtc accatggaac aaagagaaag 26160
cttttatttg ttgccgtttt tgataattct tgttatttgt tttataagtt ggcatgtttt 26220
atttatggga atattagaca tgtcttttca atgtatgtgt atgttaatta cattcataaa 26280
tattcaactt ttttttttt tttaattttc ctgcctgaaa aatttccagc ttgctgtctg 26340
tctgggcata gcgtgtgaca ttttctttgt tttagttcac tgattcctag ttggttcatc 26400
tccctcaggg aacctttgga aacatatagt agcatttttt gattgtcaca atgcctgagt 26460
atccctgcca gcatttagag ggcagaggac aggaatgcta aaccgttgca atacacagga 26520
tagttccata ctacaaagaa ttgtctgggc ttaaatgcca atagttcttt tgttgagggc 26580
ccatcttggt tgataggaag tgaatagaga ggcagaaagg gatgctattg gtaataagag 26640
cggtcataca ctgaaactta ttatatgcct gatatatagt caccatagct atagcatttg 26700
ttcttgtgac actccaggga ggtagatacc attactattc ccttttact aatgagtgaa 26760
ctgaggcaga gtaggatatt tggctctggg cctcacatac ttaactctaa tactctgttt 26820
ttccacatgc tttactttct tgtaacttta aattaataat aagaggaaaa ggagaaccac 26880
acttgctttg tgctttacag tttgttaaat atcagaatat acctcctgga aacatttctg 26940
ccagtttagt agaatattga caagttatcg cctccaagca tttttaaaaa tatggaaaat 27000
atttgatgaa attttttaa aattaggatg cctttgtaga ttggaagaaa ctcttatttg 27060
atggaaaaac agttggtgct ccataaatgc ctggggaatt gaattgactc tggaggcact 27120
tagtgtcttt agagggtgtc aaagatcttg caaatttatt ttaattttaa ttttaatttt 27180
tttttacttc acataaaaga gaatctgcct cacgtatgat ctttgtaatt tgaagacgtg 27240

ccagtgacat tgatgaagaa tgtgactttt tcttggacat gccttgcact tccctgtttc 27300
tgtgccagtt ctagtttgtt tcctctgtga ggcrtcccct cccctcagat ccatctatct 27360
gtagcttaaa tgcacctttc tctacaggac ctttcttgat atccactgaa tgttatctga 27420
acctctctta cagcatgtct cctcatgcca tgagatacaa tcatttgtgt atgtatttta 27480
tctcttcctc tagaagagta ccacctttg ggagaggcat agaacaggac cactgatgct 27540
aagagtatgc ctagctcctc tggtctcttg tgtctggcac agtgtcaggc ataagcatgc 27600
actcaagaaa tttttgttta atagaaagtc aaaagaacag catgtgttat agtaaagcaa 27660
ctccatcatg gtggggaggt aataggcatg ctctactctg ggctcctgtc gcagagagga 27720
ttttgtttgg cttgaacaag acaaacattt aattctctct tacataacca gcagtggaag 27780
gctggtctgg tggttccatg ataccattag agacacaggc tccacagtcc tctgctggtg 27840
actcccattc ctgaagtcac ctcattgtcc aaaatggctg ctgtagccat agccatcctt 27900
tctctatgcc aggtagtggg attgcagaag gagaaaggag gacatgcctt ctctgtttaa 27960
aggagacttt ccagaagtcc cacacaacac tactgcttgc atttgatctc atcgattaag 28020
rcttagtcct atgatcacat ttggctgaag tttggaaaat gtagcttttt agctcagcac 28080
atagttcacc tgagtaacac tgggttctat tactgaggag agagaggcaa atgaatgtta 28140
aagtatgcca tgactgctcc tggccaaagc tggtcgggtg acactgcaca tcttctcttc 28200
agctttgaat accacatttt gggagaggca tagaaaattt gaaccttatt tgaaagagag 28260
aaacaagaat gatgagaaaa ctggaaacaa tattatgggg gaatgatgga aaaactggag 28320
atgtttcttt tggacaagag aatagggaa caatggttag ctctccaaat atttgaggaa 28380
ctattatatg aagaaggata aaacttactc taaatgactc taagagatgg gaaagaaatt 28440
gtagatatat cgtatgcacc aaaagaatgc tggaatttga ctttagggtc acttttaacc 28500
tttgacctta tatagtacag atgcatacca tatagatgta tccataagtt tgtgcttttg 28560
aggttaaaat attrcttatt ctctggttac ttcatattgg aattctcttt actgagggtt 28620
gctatggtga taacaccctt agcagtctgc attttgaaaa gctttggact tttccttttg 28680
tgagatgtgg tctctatgtt tcccccatgc ttggcgtttt tcaaaatatc atcaagtcag 28740
aaacaatttc caaatttatc agagtgaagt gaggagaatt ttaaaattgt agatactaat 28800
aacaggggtt agtaattcta tattgtacaa ctcagtgatt caataaatat tgtcactatc 28860
aacttctttg gattaagata gctatgttta ggcaactggt tagtgttatt tagttaagca 28920
tgtatttttt aattattact aaatttctta aacacccttg aaatataatt gttgaaaatg 28980
tcttaaaaac acagctagta tcaaccagag aaataattta gcaaagagtt aatttatttc 29040
actaagtagt gatatatttt tgaaygcatg tggaatagat gtgtgcctat aaacttgact 29100
ttgtgaatta agttttattt ttctagttca gttttacttt gaatatggat atgttgttgt 29160
tttgtgaatc ttagacatca gaaagattta gttgggaaga gaagtaataa tgtaaaataa 29220
aagtaataat aaaatactca aatttctgta ttaaattagc ttttgggggа attagctaca 29280
taattaggtt attttaatag attttcaaac tgggttgcag atgatgaata tagaagagct 29340
atatatatac ataaactctc atataagcaa atatataaga agcaaaaaaa aaaccctgta 29400
gaattgagag ggagacaata tttggagttt aaaggatcag aaaacactgg cctaaaaata 29460
gtatcagtaa tcaatttta ttaaacactt actgatatgc cagacccata atcctcactc 29520
taccctcata ttaatgttat gagtaagagc tcttattatc tccgttttta gatgaggaaa 29580
ctgaggcaca gaaattaaaa tggctgtcag atagttagta agaggtggag cagtggtttg 29640
aatccctagt atatgactag aaggacttca ccctggacag ttacttggct tctaagcagt 29700
cttcgcgtgc tcttcccctt ccttgccctt ctgtaatatt atagtagttt cccagtagta 29760
tgcagcatct ggctattcag actttgtctc ttaaccttct gtggaaaagc tgttgacttt 29820
tagacatgct gggcagaatg gaagaaggaa aatacagact gttatacttg gagaaataat 29880
gatttcatat gtaacagtag ttgaatcaat aggtggacaa atttattgaa acttcttgag 29940
ttaatccagt gatggtaaac aaacacatgg ccaaatgagc actctataaa gcatgccttc 30000
tggaatgcat attgtcttgt cttgtctttt tccttccttc cttccttcct ttcctccctc 30060
cgtcttcctc ctttttttctt ttcttttctt ttctttcttt ctttctttct ttctttcttt 30120
ctttctttct ttccttcttt ctttccttct ttctttctct gtctctctta cattctatct 30180
ttctttcttt cttccttcct tttttctttc tttctttctc tttctttctt tgtttttctt 30240
tctcccttcc cttcccttcc ctccttcctt ccttcttcct ttcttttctt tcttttcttt 30300
ctctctttct ttctttcctc tcctcccctа ctccctctct tcctccttcc ctacttcccc 30360
ccatttcttt ttctctttct tttgctctgg gtttgctctg tcagtcaggc tggagtgcag 30420
tgcagtggca tgatcatagc tcactgtagc ttcaaactcc cgggygcaag cgatcctccc 30480
acctcagcct cctgaatagc taggactaca ggtgtgcacc atcacacctg gttaatttgt 30540
tttgtttttg tagatactgg ctctcactat gttgcccagg gtggtctcaa actcctgggc 30600
tcaagcgatc ctcctgcctc agcctcccaa agtgttggga ttataggcgt gagctacctt 30660
acctggcctc aagtctgttt cttgatcagt aagcctggta atattgggct gtcttgtgtg 30720
catatatgta gatgtacatg catgcataca catatattcc actttgggtg gaatggatga 30780
atcttttgtt tccagtggaa ggagttcttt gagttacaaa tagtagaata agggctttca 30840
gtttaaacag aacccacatg agtgtttcat taatcatgtt cacgtgttaa tggattctct 30900
tgaggccttt ggagtcattg ytttgcaat atttccttag ggccttttc ttcagtccag 30960
attaatctaa aatacattgc actgatccag agatgtcacc aaattctcct gaaaagccct 31020
ttgactgtat ttgggctggc ctgtgctttt atggaaaaat gctatctcac tgctgatgag 31080
gtttctggca ttagcaaaga tggccttata catggtacca caacctatgt ggtacgatgt 31140

taggagccct gataagatac tctgttcccc tacaatctgc tccatcaagc crgtgaggaa 31200
ggtatgtagg cattaggaat gcctaaaatg ccacaattag aaaattcatt ccttggaggg 31260
cttctgtttt ctgctgaaag tgcaaacacc cgtagaaggc tttaagaatc tctcaaacct 31320
tcccgtgaat aagttcacct gggagcagat ttttggggtc agggtcgtga gccatggaaa 31380
ctctggccat gtcatgggga tctgagggag agagaaggag aggattttta gacagcggtg 31440
ggggaagtca ggcggaggtg ggaccattta actagataag gctctaatcg tctcattcct 31500
ggactatcag aacagccttt taagtttaag ttgcttttcc ctctttgtaa ccttacccac 31560
caaactttgt gaagtgttga gtgcttatag taaacagagt gaacataact cttcccaggg 31620
aagaactggc tgactttagt ttcttggttt ctggaaggag atgggatagt tttattggct 31680
tgcttgagga tagccaaacg gttgtggaca agagggcttg tttcctgaca agtgttattc 31740
tgccttaaga atacaaagat aaatggtcta ccagagcttc agtacctgtt tgttgcgttg 31800
catttagttt ggagtgtttg ctctgtgcag tggagaatac tttggagggt ggtaaggtct 31860
ctctgtttca ttactggaaa agaataggag tggggtcatg gcaatggggt atttcattcc 31920
tctgtgcgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgat ggagtcttgc tctgtcaccc 31980
aggctggggt gtagtagtcc aatctcagct cactgcagcc tctgcctsct ggtttcaagt 32040
gattctcctg cctcagcctc ctgagtagct gggattacag gtgcatgcca ccgcgcctgg 32100
ctaatttttt tgtattttca gtacagatgg ggtttcacca tgttgcccag gctggtgttg 32160
aactcctgac ctccagtgat ccaactgcct cagcctccca aagtgctggg attacaggca 32220
tgagccactg cgcctggcct cattccttcg tttgcagggg ctggatgtct aggtttatgg 32280
aaatctattc tcattcaaac agaaataggg taacaactta agataataaa gtttttcttt 32340
gaatgaatta gaaaggcatt attgtatgtt attttagtca aataatattt ttgcatttat 32400
tgcattcttc tgttatataa gagaaagttt agagaattag gatagtgaat acttttaatg 32460
cttgtttttt ttttttttgt gagatgaagt ctcacttagt cacccaggct ggagtgcaat 32520
ggcactatct tggctcactg caacttctgc ctcctgggtt caggagattc tcccagctca 32580
gcctcycaag tagctgggac tacaggtgca tgccaccatg cctggctaat tttttgtatt 32640
tttagtaggg atggggtttt gccatgctgg ccaggctggt cttgaactcc tgacttcaag 32700
tgatccaccc accttggcct cccaaagtgc tgggattacg ggagtaatcc accacacctg 32760
gcctttcatg cttttaggaa aaatttgaaa ttcttttaaa crtgggtcct ggagaatcgc 32820
tgaacttcct tttttttttct tctattgaga cagaatttct ctctgctgtc tatgctgatt 32880
acagactcct gagcttaaga gatcctcctg ctatggcctc ccaaagtgct ggggttacag 32940
gcatgggcta ctgtgctggc caaacttttt gaatggaaaa ctttttagct tggtttcagt 33000
tgattaatcc tcaatttctt tatgtcctta attctatggc ttatgccaag gcatgagttg 33060
aggtcaacag aaatcctttt atgatgatag aaagataacg atgtccaagt ttaatgtaca 33120
gtataatgac ttaaggtcaa ttctgggaaa gcctgtatgt ttatcatcaa tttctttttg 33180
gtgatggaat tatacaccta cagtatttca tgtaaaactc cagaggatca cctgaaatat 33240
gaatgattta caatggacaa aataataaaa atgctcatcg taggaaaata caaaaatata 33300
taaacaagaa aataaacata aaaatgcata aacaagaaaa tagcaagttg ggagcaagct 33360
tgcttttgac tctagtttga cctgtgtttc tcagaataaa tcttgatttt cactcttgcc 33420
cttgaccgaa gactgggcca gtggaggcaa ccaccaccat ctgtgctttc agtgttgagc 33480
atcctaccaa gcaaggtggc ttagattttg aaagttttct ctcagtcaga tagtagggga 33540
acaactctta gaatgttaga attagatgag tagtgggaat gccctggaag gaaccaccct 33600
tcatggaggg acggctgtgc ttcaggcatt gtgccagagg tttacaggga cctctttaat 33660
cctcaccgta acctgatttt gcaggtcaga aattttgtag gtaagaaaac tgcatactgt 33720
atcagtttaa attcaggttc atcaagctaa accagttcag taacaaatat ttattgagtg 33780
aaggttcagt ggtaaatgag acacaaacag ttcctgccct catggaactt agagtttgga 33840
atgacacagg gacagtcagt gctttgccag agttgaaagc catgcatctc ttggctttct 33900
ggcgattgct ttttccattg gtattcttat tttagccatt cttactgaat ttaatttaaa 33960
ttttacttaa ttattataat gcctatggat ccatgttctg catattagct cactcatact 34020
catccaagac tgtaactata ggtacccaac acccagaatt gagatggcca ctgaaaactc 34080
tatncttgac caacactcta atatcatttt attttcttta attgcctttg taagaagtat 34140
aatacaaaca aaactccagt aagcaaatgg ctttaattat ttgtgtgtca gttagtagag 34200
attttattgt atatattttc tggtatagtt tattactgaa gccgtacttc tttttagcat 34260
taaaattcta aaattttatr tttataatag tgacaaaggt ttttactgta attactaatg 34320
atatttaaaa cacagattag gcaaaatctt aggaaatata ccctgctttt tttccttcca 34380
tttctggcaa tcactgcaga taaacttgta attttattca tgttgctatt aatatgggga 34440
cattataaat tcatcatgtc tgtgcagaaa cctgaacacc actttatcac acgtgggtat 34500
cagttggtga caatgtaata ttgttgattc tgtgtcaaca agctattgaa ttgtttcaag 34560
tcatcacaat cacattataa cgtgaagtga taacattgac agagcctgaa agtggtttgg 34620
agacctcctc atgctatttg agcccaggca taacaaacca gggccaaagg actcctggtg 34680
caaagataac ctgctggtga ggcatgttct gaagttcttt ttgctcagtc tgttaaaagc 34740
aatccagtag gggagacaca ggaaatttaa ggtcattcta ccatgagagt atttgcaaat 34800
ataataggtc cttctttaca gatttacaag gcaatgattt ggcattacat ttgtttctct 34860
atagggaaat taaaatcatg attatgctat attagcaaat tgcttataaa acaaattaca 34920
atttttgatt gtaggataag awgtactctt gtagcccccc ccctccctcc ctccctccct 34980
tccttccttc cttcgttcct tccttccttc cttttcttcc ttccctcctt ccttccttgt 35040

agatctcttt gtcatctttt ggacatcatc ttagtttcac acatatattc taacacatca 35100
tatatagttc gtttattgag ggtaggctgg gtactaggag gtcctgtaac aggccctggg 35160
aatacagagg tcgcttagtc tcatctgttc tgttccttat atttcacata tccaggtcgt 35220
ggcaggagaa ttttgaactt tctgcttata aaatcatttc caaggcataa cttgtcacta 35280
aaggggaaaa atacaaaaat attgtgtaaa acatcagcaa aaccagtttt taaaaaagag 35340
aatgacatat tacatttta ttaaaaatgt tgacttcagt ttactagatg attaattatc 35400
agtacttact gcccaagaaa aggcttttaa acttattgtt ggaaatcttt tggcactctt 35460
gctgcacaat atttcttaat agtttaagaa aattcttact ctgttggcag aagccataca 35520
tgcccatcac taaatggtca aggtcgaggc atgcctgtgt gtgcaactca gttattcatc 35580
taacgaatga actgtgaata aagtttagtg tttgtgtgaa taacaatgca atgagcctca 35640
ccatcaccaa gcataaacat ttctgataag agttgtcatc agagttgctt attgatgttg 35700
aagcattggt ttcgttagag taaattatgt atatatatgt gtatgtgcat gtacgtatgt 35760
gtgtgtatat atatatgtat mtacctgatc tctactttct gaaaatttac acatttagaa 35820
tgggaggtta tttagttcct agcatgtaac ttgtgactta taaacccact tarcaattac 35880
atactgcttc aatctgaatt tgggccatag ctaaataagg gtgagttgcc attttgtacc 35940
aaattgaggt taaggtgcaa gatgccaggt gtcatttaaa ccaaggctag gatgcaagat 36000
gctaggtctc atgaaattta gtgtctggac actgattgct aaccttgaca tctctccttt 36060
ctgccctctt tttctctgtc tccctttttc tttttctccc tatttttgcc tcttctctct 36120
cttctcgttt ctttagagct tgttgttact attgcgatag tcaagaacta aataatatgg 36180
agttagggag aaggaataca gcaaggtgtt tataagattc agtcaagaag gtccatttag 36240
tagttataaa taatttagcc tatgactatg gggaattacc aaatctacca attgagagtc 36300
aatttcttct cttcttgttg ctattgtcat aatttgcagt atccaactat tgttcacttg 36360
ataacctggt gatctcatct gattattaag atgaccaaaa tgaaagtgat gtttatagct 36420
ttaacatatc catgtcagtt tgatttatgg ttcaacactt ggacctaatt aatcaggaaa 36480
accctaattt gatgctgtct atcaatgcta gtctgaaaca ccattcaaaa gccttaagca 36540
agaaagctgc ctttctaaag tctctcttgt catttatttc tcatgaatgt ccattttctt 36600
ttttagtgtt tgattccact caaccatttt ccagtaattt atattgctaa tcaaaaagcc 36660
gtataggaat tctctgggtg actgggactg gaaatgtgct ctgaaatggg aatgatttgt 36720
agtttttgca cagggtgtgt caaatcatga ggtgctgaag ggcatgttat tcttstaagt 36780
agtttgattc attgggtcct tatttacctg ggcaggcagg ccatcttaaa ttttcttctg 36840
tttggatagt gttcttttca acatcctgta agtgtagctc ttttaccatg aaagatgtaa 36900
ataaccagtt agtctctagt ggggattggg gccagaggag aagaaagtct tgagcttagt 36960
ttccttccac gtgtagggaa ggttcctctc caggaacctc agtgacttag ctgatagagg 37020
aggcactgca tgagstatty agggggagca cagaaaagac tggtacaaat acactttcag 37080
tgctttgatg ctggctaaca ggaagttttc attgctcagc gttcttggta aaaacttgga 37140
cattcttttg aatgtttgag cgcttaagtg attgtcaatt tatattttta atttttgtg 37200
aatgtatgca gttgggatgg ggagaggaca tttggagaaa ttatttttt gctctgataa 37260
tgaatacgga cgggaaaagt ttgcaccaca acgcagaggt gcttatgact gtttttcata 37320
gccacaatcc tttacattaa tgatgaacta cttgaggatt tcagatgctt gtgtttttct 37380
agtgtggtcc cctcccctg aaggggtaga cctgtggacg tgtgatggaa tggagcattc 37440
cagggtgaaa caggccttcc tggaaattag attctttatc actctcccag gggagttcat 37500
ttcaagttgc tggtactagc agctgcagcg tgagattgcc caatcctagg tgctcttatt 37560
gatgggtggg aaggagtggg attgctgttt aagaaatttt attatcttta gaagggaaga 37620
atgtattatg ttttttttt ttagatgatc tctttcatgt gggctaagat aattttgagc 37680
tctgactgtc caagctgctt agaggttctg agttgttctc cactgggggt ggtactgcca 37740
ctctcaagcg gcatagatgt gcctgggagt gtttttgtca ccgtgatgtg ggggagcact 37800
actggtgttc cacaggtggg ggtcagggat gatgtacata ctgctttgac caggacagtt 37860
ctgcaagatg agtaattgtc ccaccccaaa tggcgatagy gtcctctgaa gaacctctga 37920
gaagtgtggc tttgcttata mtgttctgta gtgctgatgg actgcctgat tgtagaggtg 37980
agaggtgcat aatgaaaaaa caagtgggat gtaagagcct tgggggagaa agacaggtga 38040
ctagtgttta aatggaaatg gagaagggta gctcagttat aaatggctca gtttaaatct 38100
ctcattgctc agaattgaga ggctgctcaa gtagtacatc tcattctgct gccatttggt 38160
tattggaaag gcactttatt ttaattacta agcaaatatt taagtaatct ttgagatcaa 38220
ctatcttgag agctgactgg attctgtggc ctggatactc agaaacatcc agcttggaga 38280
ggatggtggg ggctggtcac taggatgttg ttggcaatgc cctaaggcag cggtccccaa 38340
gctttttggc accagggact ggtttcgtgg aagacaattt ttccatggac agcagggtgg 38400
tggtgggggа gggatggttt cgggatgaca ctgtttcacc tcagattatc aggcattaga 38460
ttctcataag gaatgcacaa cctagatccc tctcatgtgc agtttacaac agggtttgtg 38520
ctcctatggg aatctaatgc agccactcat ctgacaggag gyggagctca ggcactaatg 38580
ctcactcacc cgcctctcac ctgctsctgt gtagcctggt tcctagcagg ccacggacca 38640
gtaccagttt gtagcccagg gactggggac ccctccctca tggaacctgt tcgtagtttg 38700
ccatgcaagc ggacctgctt tggatgcttc tggggcagct ggaggggctg caaggtgaga 38760
cccttctctg ctagcagcct cttgcctgca cctaccagcc tgctcactgg gctcagggtt 38820
ggggtgaggt tctggggatt gaagtggagc tccaagctct tttcatggtc aaagtctgta 38880
tgctagttca ggctttacct actcagagtg atcttcactt ttaatgcagt tattgtctga 38940

gtaatcaccc tcatactcat ttgacaggca ctctttggct tggcactgaa agctcttttt 39000
ctccatcttc tcagccttgt tgcctaccac tctccaagag gtcatcactg cttgggtcat 39060
acttattaga ccctcaccca tgctaagctt ctgtcaagtt tttgttcttt tttttcttag 39120
agacaggttt caccatgttg gccaggctgg tcttgaactc ctggcctcaa gtgatctgcc 39180
tggcatggcc tcccaaagtg ctgggattac aggcgtgagt gatcacgcct ggcctgtcaa 39240
gttgttttga ccctacacac aaagcctggt ctccctcttc accttcccaa atcctgctca 39300
ttcacaaaga cccagtgtag tcttataatt ctttgtgaag acttctctga tgacaccggc 39360
ctgtagtgtt attttttcg ccaaagtcag ttagttttta ttatctccat tgcttatttg 39420
gaaccaaatt gtctgttgtc agaggcatag ctttggaatc agactgcctc agtgtaaatc 39480
tgtgctccac tacctactag ctgtgagatt tgttcaagcc ttgtcgtcct catctatgaa 39540
atggggccat tgatamcatc tcacaaagct gttgtgagga tatgtaaggt aatgcatggg 39600
aagcacttaa aatattgctg gcaagttctg ggtgaacaaa tgctgtcatt tgctttgcag 39660
gacatgaaat gatgaaataa gtacaggctc tggagtcaca caggtcctgg ggctaaatca 39720
gacttcgaca ttttctacct ttgtggccct tgggggagtt ggttaatgtc actgaggctc 39780
aggttcccct tctattaaat aagtataaat ctcacatcat acagttctga gaggatccag 39840
tggatatgta taaagcttta tatattgtat aacacatagt aggtactcag taaacaatat 39900
cagctgttgt tattgcatgg atatttaatt tataacatat aaatcacttt tgcccccaat 39960
aaacttatag gctctgtcaa aaaaggacca tatcttttta tttatttatt tatttatttc 40020
ttttttttc ttttttttt ttttttttt tttatcccgg cccgttctca atgagctgtt 40080
gggtacacct cccagacgag gtggtggctg ggcagagggg ctcctcactt cctagtaggg 40140
gtggccgggc agaggcgccc ctcacctccc ggacggggcg tctggccggg cgggggggctg 40200
acccccccac ctccctcccg gacggggcgg ctggccgggc ggggcgctga ccccccccacc 40260
tccctcccgg acggggcggc tggccgggcg gggcgctgac ccccccacct ccctcccgga 40320
cggggcggct ggcccggcag aggggctcct cacttcccag taggggcggc tgggcagagg 40380
cgcccctcac ctcctggaca gggcggctgg ctgggcgggg ggctgacccc acctccctcc 40440
cggacggggc ggctggccgg gcaggggggct gacccccccc cacctccctc ccggacgtgg 40500
ggctaacccc cccacctccc tcccggacgg ggcggctggc cgggcggggg gctgacgccc 40560
ccacctccct cctggacggg gcggctggcc gggcgggggg ctgacccccc cacctccctt 40620
cccggacggg gcggctggct gggcagaggg gctcctcact tcccagtagg ggcggccggg 40680
cagaggcgcc cctcacctcc cagacggggc ggctggccgg gcgggggggct gacccccccа 40740
cctccctccc ggacggggcg gctggccggg cggggtgctg atccccccac ctccctcccg 40800
gatgggtcgg ctggccggga gggggctgag ccccccacct ccctcccgga cggggtggct 40860
ggcccggcag aggggctcct cacttcccag taggggcagc tgggcagagg cgcccctcac 40920
ctcccggatg gggcggctgg ccgggcgggg ggctgacccc acctccctcc cggacggggc 40980
ggctggccgg gcgggggggct gacccccccа cctccctccc agacggggcg gctggccggg 41040
cggggtgctg atccccccac ctccctcccg gacggggtgg ctggcccggc agaggggctc 41100
ctcacttccc agtaggggcg gctgggcaga ggcgcccctc acctcccgga tggggcggct 41160
ggccgggcgg ggggctgacc ccacctccct cccagacggg gcggctggcc gggcgggggg 41220
ctgacccccc cacctccctc ccggacgtgg ggctgacccc cccacctccc tcccggatgg 41280
ggcggctggc caggcggggg gctgacccccc ccacctccct cctggacggg gcggctggcc 41340
gggcgggggg ctgacccccc cacctccctc ccggatgggg cggctggccg ggcgggggggc 41400
tgacccccccc acctccctcc cggactgggc ggctgccggg cggagacgct cctcacttcc 41460
cagacggggt ggctgccggg cggaggggct cctcacttct cagatggggc ggatgctggg 41520
tggagggtct cctcacttct cagacggggc ggctgggcag agacgctcct cacctcccag 41580
acggggtcgc cgccgggcag aggcactcct cacatcccag acggggcggc ggggcagagg 41640
cgctccccac atctcagacg atgggcggcc gggcagagac gctcctcact tcccagatgg 41700
gatggctgcc gggaagaggc gctcctcact tcctagatgg gatggcggcc gggcagagac 41760
gctcctcact ttccagactg ggcagccagg cagaggggct cctcacgtcc cagacgatgg 41820
gcggccaggc agagacgctc ctcacttccc agacggggtg gtggccgggc agaggctgca 41880
atctcggcac tttgggaggc caaggcaggc ggctgggaga tggaggttgt agcgagctga 41940
gatcacgcca ctgtactcca gcctgggcac cattgagcac tgagtgaacc agactccgtc 42000
tgcaatcccg gcacctcggg aggccaaggc tggcggatca ctcgcggtta ggagctggag 42060
accagcccgg ccaacacagt gaaaccccgt ctccaccaaa aaagtacgaa aaccagtcag 42120
gcgtggtggc gcgcgcctgc aatcgcaggc actcggcagg ctgaggcagg agaatcaggc 42180
agggaggttg cagtgagccg agatggcagc agtacagtcc agcttcggct cggcatcaga 42240
gggagaccgt ggaaagagag ggagagggag accgagaggg agaggggaga ggggagaggg 42300
gagaggggag aggggagagg gggagggaga gggagaggga gagggagagg gagagggaga 42360
ggcagagcaa aaaaggacca tatcttattt ttctttttc ttccactgat cctaggacaa 42420
ttgcatatag tagttatgaa tttatttgtg gctttagtga atctggcatc atattctttt 42480
ggtccttatt tatttattca tttatttttg cacttaaatg atgtgtctac atgataatgc 42540
atcaatttgc attgtgggtt ttgtccccaa atctttgact tcttgaaatg tccttatagt 42600
attgttttgc tctaagaaaa catcagggct ctgaatcaat aattgggaca aagcagtcta 42660
ttcagtggtt tgtaaactgg attaaaaaaa aaacccaaaa gaattcctgc cacctatttg 42720
atgatctgta aggaaaacca gacagttaaa atgttgcaca gaaagagact agcaggttgg 42780
tttgctgttc ctgtcttgtt tcagtttcat taactgaatc cttgactatt ctatcaattt 42840

gacactagac agggtagagt gctccataca atttgttacc cttggctatc atcactatag 42900
tgtaaagttt tggaaataag caggtgactc taaatcttca aaaggggact ggccttgttt 42960
atgtgggcaa ggtatgggaa ttgtagtgaa ctgtcagcca acttatgaat atcagaagga 43020
tgtctatcca taccaaagga atcaaaatta agtatagaaa aagtgaagca aaaattatgg 43080
ataagttaag gaattgcctc ttaaatttgt ttgtttcttt gagttcagtg aaggtggaac 43140
tattaaaatg tgatttactc atacaaattt ttaaaaagag gactgtacct cctcaggtag 43200
accaagtgtt tggaaggacc agcatgtgtt aagaggatct agcggggaaa taggatttgc 43260
cacagaaatt accttactct gttaactttg gacaatgttc cattgactac cacttgtctt 43320
tgtcttataa gaatagaatt katggaagga gaaagaaact tacaaggaac gggtaaaaga 43380
atgaaactgc tattaatatg actcaatgtt tttttctttc ttttttttt ttttgaaaa 43440
aaacttctag atattcccct tttttcagat tattccagat tccatttttc tttctatgga 43500
tttaagatgg taaatttcta tttaaagtct cattgtttgc tctgatagct ttctatatct 43560
ctgatatata atggtctcag caggctgagt tttacaaaga gaattctaca cttcctgacg 43620
aacatgcatt agctattcca taagcacccg gtgctgtgcc agaggctgta aatgacacag 43680
aggaatgctc tcaatccagy gttgttcctt gctgtggaaa acaaacaggc aaatgactyc 43740
tcttctctgg gcgctatctg ttactctaat atcttatctt aacacattct tagtccaaca 43800
cttacccagg aagcttggga tatggctact tatgaagaaa ggattactct ttttttttt 43860
ttttccccta gctttgggct ctttatgagg ttggaaaaca agtttattcc tatgtctaat 43920
aaaatttttac taccgatttc aaaacgctta aatttttttt gcattgcttt caattgctgc 43980
aatttttcct aagcccaata atttttttaat gctatgttag tcaccaagta aactactctt 44040
tttctccaac tgaagtatat aagcactatg gattctatgc cagcccaata atgaactcaa 44100
ttaatgttaa ttgagagcag ctttgggggga aaaaaatcag atttttacat tcattcttga 44160
gtttagtgga ataaactttt ttttttggtg aaagggaaca tagagtagtg gtcaagtagc 44220
acgaatgctg gaatcagagc tgtcagattc aaatccttgc tttgcacata tttgctgttg 44280
gatcttgggc aagttaccga attgctctgt gcttcaattt atttatttgt aaaatattca 44340
taataacagt atctatttca tagggttatt atgaggatta aatgagctaa tgttggcaga 44400
gcacttagaa tggtgtgtgc catttaagtg ctatatgagt acttcttttc atctttgcac 44460
catctattct gattgatggg acagacaggg gctagtgctg gagagatagg gtgttcattt 44520
ggttccgatg gttcctttgt gatgattgcc tggttcttaa caaaaggttt ttatttcaat 44580
gtggattgta ttttcctcct ttcctccttg gtttttacta gagggatttt ttttttttt 44640
aatcaggcag cccccaaacc agagaggctc ctggagaatg ttttaaagtt acataaatga 44700
ttatttgcaa gattacttct tggctaaaac tggattggtt gaatgtggca gttttgagac 44760
tattttctga acaaagtttt aaagctggyt ctatgtagat ttttttttc tccctgtggg 44820
tggctccaat gtatgaaatc atccccttag cttttttttt ttttaaatct tcaaataaat 44880
aacaaaatgt agataatatc tagataaaac ttttggaggg cttgtgagta aaggctactt 44940
atttaaaaca aaacactcaa aataaattgc atatagacta attgaagtaa ggggcacctg 45000
caattgttat tagacctaat ctagaccttt tcactagtgg tttatttttg gtttattttt 45060
aaacaacaca tattcccttt atgagagaat gagcttctga ggccagtgaa gcattttggc 45120
tgatggctga gaggtcaccc agcaatgata aagtatcagt ttgtttttc tggagagata 45180
tttccaaaca atagtcgttt gggagttata aacaggcatc gaagttamta ctgaaaaggt 45240
gaatttgaca aatgaattat agatctgttg ataaattgag taaattggat ttgatatatt 45300
agataatgga gtgaggagat caagtgtgaa aatcactacc tataaaaatt asttaattgc 45360
aacatttccc catcagtttc atttttcata tgtgtgattt taaataattg actttgaagt 45420
gttttataaa atgacttttg rgtctctatt ttgtgttctt ttcatgatgt gtttaacttg 45480
gtattttagt ttggcaaaaa caaacaaatc cccccacccc actcctcaaa aatgggactt 45540
gtaataaaag ttgcttaaga aatagcatta attatatata ttttcaaaac aggcaatata 45600
tattgttctg ataatttcct cctaaatact cagtctctaa atttatattt ttcttttctc 45660
catagcaata tgaaactgtc tgtaagagga ctgttcttta tgattgttat aatttttcaa 45720
ccagaagata ctacctttac aacctcagat actaagggag acaaatgtac tgaacttaca 45780
aatgtattat gttggattac taacaataga cctaattgat aaaagtgatt taatatatgt 45840
tgtgttaata gctaaacctc caaagcccct aatctcccat ggaaatattg ctttgtagaa 45900
caaaatccaa tgagaagttc tgggattcca gagtgaattt gtacattcct taggggcatt 45960
tttgcaaggg aggttgttgt gttttaaagg tagttgataa gagacctgca ccaccaaccc 46020
cagacctrca ccaccaacca ccatcatgca ttagtctata gaaggtattt gggtgtacgt 46080
actcctgtac cactcggtac caccatttag ccaagcgaag tttctgacca tttgcagcat 46140
acattataaa tcaggatgtc actaccagac aatcagattt gaacattcca tgaacaaagt 46200
agcctatata ccctagaaat agatcactta actatgttta tgtcatgctg ttgatatgcc 46260
tgcatttaca caaatcagga tagcacattg cttatttatt ttaggagtag gtacttgatc 46320
tgtatattta cctaattttg gttaattagc caaaaattga aatgggtaat ttagcatgat 46380
tgcttaaata catggggaag atataattat tcttccaact gcaaaaattt ctcctttatc 46440
ccttgggttt gtgaaagaat aaaataattt tgagtcttct ctaagtgggg ctggtagtgg 46500
ctgctttctt tgaaaaattt ttctatgtgg cacataatgc ttgggaaggt cactggccag 46560
gtatttgggg aactttgtcc cttggggaga cctaggaaaa tcacaggata tattagttca 46620
gtgaagtgag cttgtttaag ttatattgtc cttccagtat cactagggac tatcactgcc 46680
acttggggtg tcaacttttg gtgtcaagtt tgtatactct tgttggctgc agagattttg 46740

ttttgttttg tttttggctc tttggtttaa aaaaaattgt ttgcagagat gagcttatag 46800
atctggcaag ttataattta atttttaaaa attaagacaa aatattagtc tgaatctaag 46860
aatgaaaggc cataacttgc tatatatgat ttagtaataa aaaatcactt aaaaaataag 46920
gtgaggaact caagaaagta tagtcaagca aatgaaaagt tactcacgat gttatcaatc 46980
agagataacc actgttaaca ttctggtctt ttttacgctt ttttttttt tgcatatgta 47040
actctgttat cagtaaaaat ttacgtcctt gtttttgtta cattaaatta taagtatttc 47100
tctaagtact tagaatttct ccataaccat tttttaagtt actaatatgt caatataaag 47160
atgtaaacaa atttaatcct tttattgttg gacatttagg aggtttgcaa cttcctttgt 47220
tataaataat gttgcgatga aaatctttat acataaatct ttgtctactt ctttgattag 47280
ttccttagga aaaaaatcct tgaagtaaaa gtactaaatt aaagatcaag tatttttaaa 47340
aagcaagata cgtgttgtca aactgctttc ccaatgagtt ccatcaagat acacactaat 47400
caactgtgta tgaaaatcac tttcttccca cggatgttca aataaatatt tttatattat 47460
cattgggaga atgtttacct aattttctaa tttgcatttc tttgattatc taattagttg 47520
aataattttt cattttatca aaaatttata tttcttcggt taaatatctg catggcataa 47580
gtttttaaaa tttctgtcta ttattgcaga atgtgacagt gcgcattttc gctgtggaag 47640
tgggcattgc atccctgcag actggaggtg tgatgggacc aaagactgtt cagatgacgc 47700
ggatgaaatt ggctgcggta agtgaggagg ggccaggcta agttctattt tgagtaacct 47760
aagtgcttcc tggtgatttc agctgtaaca aagagaagag ctatgccttt tagtgacaga 47820
gccaggtctg ggcccaagtc ttttgagatc tgtgtggttg aatagagaac tgatggcatt 47880
aacaataatt tcactccctt ctgaggtagg ggttcaattc acattgatga tagagcatca 47940
gtttctatct caccctttatc ccttgaccac aactttgata tggaaacata tttgggtgca 48000
gttttctgga gtctgtaggt gattatttct aatattcact ctgtaaattt tgtgtaccca 48060
caagaacaaa caaaaaataa tgttatctga actactgtga tttgtaagtc aaagaggagt 48120
ccatttttat gtaaaggatg tagaataact tgtgtcaatt accataaaga aatcacagaa 48180
ttggttagtg tgatttatgt tttttaaaaa ttctagtttt aaaaaatttg aaaaatacga 48240
taatgtagta aacttcaaat ctaattaatt ataaaatgac tttcacattc attttktcat 48300
ttagttttct cactaatctt ctgaggtcgg tttcagatta gtaaattgag actcggagaa 48360
gttaagtcat ttattaaagt tcttacagtt ggtaagtcta tgcacagatc ccattgctct 48420
tcccaacttc ccataggtga tcaatcatac atctgcaatt tccttcatcc cagcaggtga 48480
actaatgagg gttatctttc aaaaatcagg aaagcaggtg aaaaattttt gttttgaatt 48540
gttggccatg ttatggcata ccatagcagt caaactttgg tgtgtcattt agatgacaac 48600
gcatttgaaa atgggaggaa gggtaaggat ggggttctgt acagtgctcc tcaaatactc 48660
atgcacaaat ggatcaccca ggagctcatt aaagtgcaaa tttagattcc atattttgag 48720
gtgggacctc agcttctgcg tttctataaa cttcctgatg atgttgatgc tgctagtttg 48780
tggactgcac tttgaacaag ggactaaact atatttgtag agacacaatc atgtgctaac 48840
tatttgcctc ctctgggctt actgagttca ttttgattaa acaataaaag caaaaaggca 48900
agggcagtgt atctggggta aaggaataag tgaacagcta tgccaacarc tcttcagaga 48960
ttgttacctg tattatattt tattgacctg taaaaataat aacaataaca acaatatcaa 49020
tgacgatagt gatagcaagt aacattacat ggcgctttca catacattat ttaacttatt 49080
tttcacaaca aacagtgaga tgagtatagt ccccatttta tgatgcatac attgaggttc 49140
agagaacctg ccaaagatct taaaggaagt aaatcatgga aataataatt atttgatttt 49200
gggttttctt tcccaaatct catgaatttt ccagttcatc atgatacttt actattagtt 49260
attatgaaac aaatagttta acagtaactc acagttaatg tttacttgaa tgaagctttt 49320
aatctaatac ctttatcata attttttttgt gtgtatgtgt gctgtttgtt ttattctctg 49380
tgtttttaag ttgctttggt tcatgagttt gttgtgatgc tgttgctgag cttatttgac 49440
agtgaactct gactggcgtc cacagactct agtrtaaggg ttgtttacta tttgccttca 49500
aataaattga gcaggagttt acatgataca ctcttctgga acaagcattg cttgctagta 49560
taatggggag gatgattgcc ataatgagtc ctcttttggt ttgttttagc tgttgtgacc 49620
tgccagcagg gctatttcaa gtgccagagt gagggacaat gcatccccar ctcctgggtg 49680
tgtgaccaag atcaagactg tgatgatggc tcagatgaac rtcaagattg ctgtaagtgt 49740
ttggagagga atcttgcttt ggctttgtgg acacctaaaa cccaacctgt cgcaaagaag 49800
ttacacacaa tgggatgatt ctttataaat gtggagcagg gccttaaatc ataagggaac 49860
ctatgccagc aatctcattc aggggttgga tgatrttgaa agtacggatg tactgaagaa 49920
ttatgaatat accccagcaa tttggaagtg agataggttc ccaatcttta attttgatta 49980
tgttatgctc aagaaaggaa ccaaatattt attggagtgt atagctgggt gtcttcatgt 50040
gtgtggttga cagctgaatg agtcctttgg ctctgtggca tactttgtat tcaaaccttc 50100
cactccttct gccccaatat taaattctct tctttttgac tgagtggaag taggtaggtt 50160
tgttggaggg cttcttggtg gttacttcag tgactgctgc cacagccacc atagggagag 50220
cttgaacaag aaagaaaata gtagcgatga agcggatctt ggcaactgcg gcatccctgg 50280
acrttgaggg ggtttggttc agtaacctgg aaaaaacctt taaattctaa tttctttgga 50340
atcagactgg aaaagactgt tttaataggt ctaacaataa ttttatttta tttattttwa 50400
ttttattatt atttttagag tcagggtctc actctctcac ccaggctgga gtgcagtggt 50460
gcgatcacag ctcactgcag cctcaaacac cggggctcag gtaatcctcc tgcttaagcc 50520
tcctgagtag ctgggactat aggtgtgcac caccatgccc agctaatttt taaatttttt 50580
gtagagacac gatcttgtta cgttkcccag gctggtctgr aatcctgggc taaagtgatc 50640

```
ctcctgcctt ggcctcccaa aatkttggga ttataggcat gacccccca tgactggcct 50700
gaaaataatt ttagatgaga agtaatgttg ggtaaatata agatggcgac ctatgagcaa 50760
tttgtctatc acatgtatca ttccattcct ttctctatta aggatatttg tataatttaa 50820
aatcattctt gtatcattgt ggatgttttt ggctgcaagg aaagaaaaca caactcaaaa 50880
aagttaaaca aaaaggggat ttattatctc acataataag aagcctaact atagggttgt 50940
tccagggttg attaattccc agctcagaaa tattatccag ctttttctca ctttttgct 51000
ctgccatatt tatcctattg gcctttcttg attgcataaa agctgctcaa gtctcaaaat 51060
ttgcatcctg aaggcctgac attctctcag gcagagagga ggttcttaat agatagatac 51120
taaatgcata aatgatgggt tgttcatctt taggctatat agttttgagt ctattttctc 51180
ttactcctct cacagagtgg gaagaaagct gagctttatt ttgcgattca atgtgtggtg 51240
gatgaccctt tgctaataat aatactttac agaggggatt ggaactacta agggcaactg 51300
cttgggaaaa gagactggag ataagtttat agcagtcatt ttaaaacaat attgcatatc 51360
attttaaatg actatacatt tcatgaggca attctcccat ttttaatgat ataaaaattc 51420
tccattagat atcttttaac cacaaacaaa atatgccacc tctgtattca ctaaagttac 51480
cagataactc ctgattgcca atgggcactt ttccttcctt ctcacactgg atgggcrttt 51540
agattgcact tgactctgga gaccattcct ccttcttgac accactccct tggctgccat 51600
gactcccagc agtcctggct ctcttttgag ctgctttggt cattccattt tattttcctc 51660
ttctactcag cccttgagta ttggtgttgc tcagagccct gccctgagca gcttttctca 51720
ttctggacac tctcaggata gtctcaccat tctcatgact ttagtgaccc tctgtggcct 51780
gatgagactt aaatctgtgt ttacaaccca gatttttgcc cacacttgag tcttgtatas 51840
tcaactacct ttggacctct gcaagttgcc ttgaactcaa ggtgtcmcaa ctgaaaataa 51900
tcatcttccc tcctgaactg gattttcctt ctatatttgc tagtctacat attttatctt 51960
tattaataga aatagcattt aacccactat gaggcactgg cagaaaatac aaaatcagtc 52020
ttaaactatt ggaaataggc agatggaggc tctcttactt gttgaatttg tgaaacatat 52080
ttcataatga aagtatttta ttagatgaag aagaaagatt gctgtaagtg acaggaaaga 52140
tataatcaat taacatgaaa aggctatcac aatcccctag gcacccacgc tagaaacttg 52200
gaggttattc ttgattcctt cctctttttc actgcccaca ttgaatcacc aactcctgcc 52260
taatttgcct cataaatatt tctaaagtta atctcttcat ttctctctct tttatttta 52320
ttttttggca aggacagatt ttttttttt ttgagacagg gtcttgctct gttgcccagg 52380
ctggaatgca gtggtgcaat catggctcac tgtagccttg acctcctggg ctcaaatggt 52440
cctcccactt ctcagcctcc agagtagctg ggactacggg cgcatggcac catacctggc 52500
taattttgta ttttttttt ttttttttt ttttgtagag atggggtttt cccatgttgc 52560
ccaggctggt ctccaactcc tggcctgaag tgatccaccc accttggccy cccaagtgct 52620
ggratgatag gtgtsagcca ccatgtctga cccatctctt tatttctgct cccactgcca 52680
acatctctca tttgggtgtc agcagtagtc tctgggttgg cctccctgcc tccagttctg 52740
tggatcctta gattctctct gacactgatg ctgatctaac taagattctt tggtagctct 52800
ccattaattc caggagaaag ttccaattcc ctaacacggt ttacagtggc ttccaagatg 52860
tgactagtgc ttattttcct atgtctatca tttgctattc ttgccttgaa gtggccactt 52920
gggcacagca gtgcttttag ttcctgtggg tgtgccatgc tgtgtcctag ccttttgtct 52980
ccgtgcaagc tggctgaatg ctgaatgctc ggttctagac agtccttctt tgcttttggc 53040
ctacctgact gctgcttctt taagacccag ggaggtgtca ctttttcaag gaaactgtcc 53100
ccatccatgc tcccatccca gagtgaatta agttcctgga ttgatggttc tatcattcct 53160
gtgtgcctat aatccacttt cataattgtt ttctaattac tccttagtgt cccctagaag 53220
actatgagct tcttgagggt agggattgtg ccttattcat ttgcagatcc ccatattgct 53280
atactgtgtg gtacattata ggccctcaac agatgtttgt gtaattaatg aatagatgaa 53340
tctcagcatt agataggttg atggaattat ataattttaa tttgtttgct ctctacattt 53400
gaatgagctt ttaattgctt cttcgtaagc cctttgaaaa cctaagcaca acatttagaa 53460
ttatttgggc ttgacgtaaa gaagaaagcc aaggtaattg aaygagcact gatacctgac 53520
ccaggttctt ttcatatttt gtttgagaca acccatgact tgccttctcg ggaataaaag 53580
aaagttcttt aattttatgt gaaaattggc aatatatact taaataaatt atttggaaat 53640
ttaatgagga agtattaatc tctttaacct ttttcagata aaattgtgtc tctgccatgg 53700
gcagaattca gacacttaag tgccttctgg aaaaatctat ctattctgcc tttattaata 53760
gaagtaaaat tggacccaca ggtataaggt acttagagaa aataygaaat tatttagtgt 53820
tagaagtagg ctgacttgaa aaattttgtt tgctgttcca gaattataag acaccrtttt 53880
gctaattaaa cagaaagaag gaacaaaatg acaaggaaga tataatcaat taagcatgga 53940
gaagggtgtt aattatggtt ttataattat tatatcttat cacatgataa tttctatatg 54000
tttgaatttt caagtaccac cttgaaaact gtcactgtct acttatcttt tacatatttt 54060
ttttttttta gagacagggg tcttgctttg ctgcccaggc tggagtgcag tggcatgatt 54120
atagctcact ctaactacat aaaaagagaa gtttttttg gctcaagtga tcctcctacc 54180
tcagccttcc aaatagctac gactacagct acttggaagt gagccactgt gcccagctaa 54240
atttwwtttt tttttytttt aagatataag gatctcacta tgttgcccag gctagtcttg 54300
aattcttggc ctcaagtgat cttcttgcct caatctccca tagctgggat taaaggcacg 54360
agccactgtg ccaggtttac ttgtcgtttg aaaaggtttt tcatgttaag ttttgggggt 54420
acattcctta acagatctaa ttttatcaga aaaccaagtt ttgctgaacc taaatatcta 54480
tactacatat aagtaaaaga agckctgtag gctgggagcc tcggatccct gacagttttg 54540
```

cagaacgctg atatctatgg actctaaaat agacttcatt tatagatacc cacggaccac 54600
taatggacaa aaacatgaat caatatgtat tgtggcattc aaatcctagc gctttgggag 54660
aggagggagg ttccaagatg gccgaatagg aacagctcca gtctacagct cccagcgtga 54720
gcaacataga agacgggtga tttctgcatt tccaactgag ctttgaagag agtagtggat 54780
ctcccagcac agagtttgag atctgagaat ggacagacta cctcaagtgg gtccctgacc 54840
cccgagtagc ctaactggga gacacctccc agtaggggcc gactgacacc ggatacggcc 54900
aggtgcccct ctgagacgaa gcttccagag gaacgatcag gaagtaacat ttgctgttct 54960
gcaatatttg cagttctgca gactccactg atgataccca ggcaaacagg gtctggagtg 55020
gacctccagc aaactccaac agacctgcag ctgagggtcc tgatggttag aaggaaaact 55080
aacaaacaga aagggcatct acaccaagac cccatctgta catcaccatc atcaaagacc 55140
aaaggtagat aaaatcacaa agatggggag aaaccagagc agaaaagctg aaaattctaa 55200
aaatcagagc acctcttctc cttcaaagga acgcagctcc tcaccagcaa cagaacaaag 55260
ctggatggag agtgactttg agagttgaga gaagaaggct tcagacgatc ggtaataaca 55320
aacttcccca agctaaaggg ggatgttcaa acccatcgca aagaagctaa aaatcttgaa 55380
aaaagattag atgaatggct aactagaata accagcatag agaagacctt aaatgacctg 55440
atggagctga aaaccatggc aygagaacta cgtgatgcat gcacaagcgt caatagccgt 55500
ttcgatcaac tggaataaag ggtatcagtg attgaagatc aaatgaatga aatgaagtga 55560
gaagagcagt ttagagaaaa aagagtaaaa agaaatgaac aaagcctcca agaaatatgg 55620
gactatgtga aacgaccaaa tctacgtctg attgttgtac ctgaaagtga cggggagaat 55680
ggaaccaagt tggaaaacac tctgcaggat attatccggg agaacttccc caacctagca 55740
aggcaggcca acactcaaat tcaggaaata cagagaatgc cacaaagaca tacctcgaga 55800
agagcaactc caagacacgt aattgtcaga ttcaccaaag tttaaatgaa ggaaaaaatg 55860
ttaagggcag ccagagagaa aggtcgggtt acccacaaag ggaagcccat cagactaaca 55920
gctgatctct cggcagaaac tccacaagcc agaagagagg gggggccaat attcaacatt 55980
cttaaagaaa agaattttca acccagaatt tcatatccag ccaaactaag cttcataagt 56040
gaaggacaaa taaaatcctt tacagacaag caaatgctga gagattttgt caccaccagg 56100
cctaccttac aagaaatcct gaaggaagca ctaaacatgg aaaggaacaa ctggtaccag 56160
ccactgcaaa aacatgccaa attstaaaga ccatcaaggc taggaagaaa ctgcatcaac 56220
taacgagcaa aataaccagc taacatcata atgacaggat caaattcaca cataacaata 56280
ttaaccttaa atgtaaatgg gctaaatgct ccaattaaaa gacacagact ggcaaattgg 56340
ataaagagtc aagacccatc agtgtgctgt attcaggaaa cccatctcac gtgcagagac 56400
acacataggc tcaaaataaa gggatggagg aagatctacc aagcaaatgg aaaacacaaa 56460
aaaaggcagg ggttgcaatc ctagtctctg ataaaacaga ctttaaacca acaaagatca 56520
gaagagacaa agaaggccat tacgtaatgg taaagggatc cagtcaacaa gaagagctaa 56580
ctatcctaaa tatatatgca cccaatacag gagcacccag attcataaag caagtcctta 56640
gagacctaca aagacactta gactcccaca caataataat gggagacttt aacaccccac 56700
tgtcaacatt agacagatcc acgagacaga aagttaacaa agatttccag gaattgaact 56760
sagctctgca ccaagcagac ctaatagaca tctacagaac tctccacccc aaatcaacag 56820
aatatacatt cctctcagca ccacattgca cttatttcaa tattgaccac atagttggaa 56880
gtaaagcact ccccatcaaa tgtaaaagga cagaaattat aacaaactgt ctctcagacc 56940
acagtgcaat caaactaraa ctcaggatta agaaactcac tcaaaaccgc tcaactacat 57000
ggaaactgaa caacctgctc ctgaatgact actgggtaca taaagaaatg aaggcagaaa 57060
taaagatgtt ctttgaaacc aatgagaaca aagacacaac ataccagaat ctctgggaca 57120
cacttaaagc gtgtgtagag ggaaatttat agcactaaat gcccacaaga gaaagcagga 57180
aagatctaaa attgacaccc taacatcaca attaaaagaa ctagagaagc cagagcaaac 57240
acattcaaaa gctagcagaa ggcaagaaat aactaagatc agagcagaac tgaaggagat 57300
ggagacacaa aaaacccttc aaaaaatcaa tgaatccagg agctggtttt ttgaaaagat 57360
caacaaaatt gatagaccac taggaagact aataacgaaa aaagagagaa gaatcaaata 57420
gacacaataa aaaatgataa aggggatatc accaccaatc cctcagaaat acaaactacc 57480
atcagagaat actataaaaa cctctatgca aatcaactag aaaatctaga agaaatggat 57540
aaattccttg acacatacgc cctcccaaga ctaaaccagg aagaagttga atccctgaat 57600
agtccaataa caggctctga aattgaggca ataattaaga ggctaccaac caaaagaagt 57660
ccaggaccag actgattcac agccgaattc taccagaggt acaaggagga gctggtacca 57720
ttccttctga aacttttcca atcaaaagaa aaagagggaa tcctccctaa ttcattttat 57780
gaggccagca tcatcctgat accaaagcct ggcagagaca caacaaaaaa agagaatttt 57840
agaccaatag ccctgatgaa catcgatgca aaaatcttca gtgaaatact ggcaaaccca 57900
atccagcagc acatcaaaaa gtttatccac catgatcaag ttggtttcat ccctgggatg 57960
caaggctggt tcaacatacg caaatcaata agcgtaatcc atcatataaa cagaaccaaa 58020
gacaaaaacc acatgattat ctcaatagac gcagaaaagg cctttgacaa aattcaacag 58080
cccttcatgc taaaaactct caataaatta ggtatcaatg ggacgtatct caaaataata 58140
agagctattt atgacaaacc cacagccaat atcatcctga atgggcaaaa actgggagca 58200
ttccctttga aaactgtcac cactcttatt caacatagtg ttggaagttc tggccagggc 58260
aatcaggcag gagaaagaaa taaagggtat ccaattagga aaagaggaag tcaaattgtc 58320
cccgtttgca gatgacatga ttgtatattt agaaaacccc atcgtctcag cccaaaatct 58380
ccttaagctg ataagcaact tcagcaaagt ctcaggatac aaaatcaatg tgcaaaaatc 58440

acaagcattc ctatatacca ataacagaca aacagagagc caaatcatga gtgaattccc 58500
attcacaatt gcttcaaaga gaataaaata cctaggaatc caacttacaa gggatgtgaa 58560
ggacctcttc aaggagarct acaaaccatt ctcagtgaaa taaaagagga cacaaacaaa 58620
tgaaggaaca ttctatgctt atggatagga agaatcaata tcatggaaat ggccatactg 58680
cccaaggtaa tttatagatt caatgccatc cccatcaagc taccaatgac tttcttcaca 58740
gaattggaaa aaactacttt aaagttcata tggaaccaaa aaagagccca cattgccaag 58800
acaatcctaa gccaaaagaa caaagctgga ggcatcatgc tacctgactt caaactatac 58860
tacaaggcta cagtaaccaa aacagcatgg tactggtacc aaaacacaga tatagaccaa 58920
tggaacagaa tagagccctc agaaataata ccacacatct acaaccatct gatctttgac 58980
aaacctgaca aaaacaagaa acgggaaaag gattccctat ttaatacatg gtgttgggaa 59040
aactggctag ccatatgtag aaagctgaaa ctggatccct tccttacacc ttatacaaaa 59100
attaattcaa gatggattaa agacttaaat gtcagaccta aaaccataaa aaccctagaa 59160
gaaaacctag gcaataccat tcaggacata gacatgggca aggacttcat gtctaaaaca 59220
ccaaaagcaa tggtaacaaa agccaaaatt gataaatggg atctcattaa actaaagagt 59280
ttctgcacag caatagaaac taccatcaga gtgaacaggc aacctataga atgggagaaa 59340
atttttgcaa tctacccatc tgacaaaggg ctgatatcca gaatctacaa agaacttaaa 59400
caaatgtaca agaaaaaaac aaacaacccc atcaaaaagt gggcaaagga catgaacaga 59460
cacttctcaa aagaagacat ttatgcagcc aacagacaca tgaaaaaatg ctgatcatca 59520
ctgagcatca gagaaatgca aatcaaaacc acaatgagat atcatctcac accagttaga 59580
atggtgatca ttaaaaagtc aagaaacaac aggtgctgga gaggatgtgg agaaatagga 59640
acacttttac actgttggtg ggactgtaaa ctagttcaac cattgtggaa gacagtgtgg 59700
cgattcctca aggatctaga actagaaata ccatttgacc cagccatccc attactgagt 59760
atatacccaa aggattataa atcatgctgc tataaagaca catgcacaca tatgtttttt 59820
gtggcactat tcacaatagc aaagacttgg gaccaaccca aaagtccatc aatgatacac 59880
tggattaaga aaatgtggca catatacacc atggaatact atgcagccgt aaaaaaggat 59940
gagttcctgt cctttgtagg gacatggatg aagctggaaa cgatcattct gagcaaacta 60000
tcgcaaggac agaaaaccaa acaccgcatg ttctcactca taggtgggaa ttgaacaatg 60060
agagcacctg gacacaggat ggggaacatc acaaactggg tcctgtcgtg gggtagggga 60120
gaggggaagg ataacattag gagatacacc taacgtaaat gactagttaa tgggggcagc 60180
acaccaacat ggcagatgta tacatatgta acaaacctgc acgctgtgca catgtacccc 60240
agaacttaaa gtaaaataat aataataaaa aaggaattat aaaaaaaaga agttttgtaa 60300
aaattgagag saaatctttt ttcttccatt aggggattat attatatttt ttagatgatc 60360
acgttttccc ccaaagctct ttgtatgtag acaatttaaa atcccaggat aagataatgt 60420
taccatgtta tggtaattcc tgcctcagat ttacaggata gctttcacat catgcttgcg 60480
ggcatcagtt cactggattt tatctgtttt atccggaggc aaatttcatg aactgctgat 60540
gccctgcttt cacctatact aatcaacatg ggatgaaatc aagstagctt aaatttttt 60600
ctctttataa aattgataca tggtcaatgt aggcagttta tagaatagag gaaactatat 60660
agaaaaaaat aaaatcactc atattcatat tcacaccact ctggaataac tgctattaaa 60720
gctttggtat atttccttct tgtttataca aggatttcaa tgggtgggtt gggggtcctt 60780
ggttaatacc tatacttgca aaatttttat ttcattaaac tttttaccat atagttttaa 60840
aatctatatt gtattcttta cacatgttga taacgtaatt gtgtacatag catgcttgag 60900
tgtggacact attctctggg cattttgata ayattatact tctgtttttg ctttgtaagc 60960
tcagcttggt ggtagccagg tactttacct tgtgtcccta tgaactttwt gctttccaat 61020
atccttgtta atgmcaatag attagtctgt gtctagcaat aattataaat taagtaataa 61080
ttttttctct tcgcagcaca aagtacatgc tcaagtcatc agataacatg ctccaatggt 61140
cagtgtatcc caagtgaata caggtgcgac cacgtcrgag actgcccmga tggagctgat 61200
gagaatgact gccgtgagtc tgttttagtc cttgcrctgt atttggtttc accttgtcc 61260
ctttggcatt ttaatcaatt tgttagattt gttgatggac rtaaatgcct acaatatgcc 61320
tcttgttatt gcaatctctt ggcagattct tttgtggatt aggggtgatg ttctgataag 61380
agtctatttt taacaagaca ttctaagagt gtcctgcctt agtgcatcaa gtttctgtat 61440
tttttatagt aagaaacttt taacatgaac atagattctg aaaggaagga taattaaata 61500
cattgagtac agaatcaagt ttggtaaatt ttaactgtta ttacacagct atagtaagtt 61560
tctaggtcaa atttctcact agttttcctg cttttatgaa ctcaacattt ttcagattac 61620
ctttggaaaa gtgttacatt ttgaaaatgt cttttcctat aacagcagca tactatatct 61680
ctttgtaact gatcaccaca aaataagaca tataaatcat agtattctat gtataatgta 61740
taaatattac cacaccaaaa taagaaagtg caatcatggt tcattatcta gtaacaggta 61800
agtaaagaac aatcttcctc tttcgaggct tatatagaag tgttaggata tgagaagata 61860
ggaattagtc tgctgtgtca gtcctatagt ccatataatt gtctttaatc tcaggcatac 61920
cacagtttct ctctctttct gtttttttatt ttttattttt gagaaggagt ttcactcttg 61980
ttgcccaggc tgagtgtgat ggcatgctct cggctcaccg caacctccac ctcccaggtt 62040
caagcgattc tcctgcctca gcctcccgag tagctgggat tacaggcatg cgccaccacg 62100
cccgactaat ttttgtattt ttagtagaga tggcatttca ccatgttggt caggctggtg 62160
ttgaacttct gacctcaggt gatccacccg cctcggcctc ccaaagtgct gggattacag 62220
gcatgagcca ctgtgtctgg cccctagttt ctctgaaaag ttcttacaag tctagcgttt 62280
atgaattttt ccagaagttc cttgagtttt taatatatat ayattttaat atatacatat 62340

aacatatatt tctgacaggc cttttcgtgc agtcctgcat ttcataaatt tactatgtgc 62400
tgtataaaga tatagtcatg tgtcatttaa tgagggggac acattctgag aaatgtatta 62460
ttaggcaatt ttgttgttgt gtgaacgtga tagagtgttg ttaaacaaac ctggatggta 62520
tagcytactg cacacctagg gtaaacagta tataccctag gcatatactg ttgctcctag 62580
gctacaaacc tgaacaccat gttyccgtgc taaatactac aggcaattgg aacacaatgt 62640
taagtattta tgtagctaaa catatgtaaa catagaaaag gtacagcaaa aatatggtat 62700
tataatctta ggggaccact gtagtacatg tagtccatgc ggtctgtcgt tgaccgaaag 62760
agccatatgc ggttcctgac tgtasttcct tttgtttgct cttaaattta tatttcaaac 62820
ttcaagaaat tatcccagta ttccattaat tggtgagcag atttttgtgt accttagaaa 62880
tcttgatcat aaacttttca gttattatgt ctccaacgga agattcaagt tttagcctat 62940
tctcacggga tatctcctct attgttttat aattttgatt taattttagt tctctggatt 63000
gtctctaaat tccttccttt gatacaaatg gtttatttta tgctttctga taaaagaact 63060
atcttgtgta aattttgcta aacttcccaa tatggtgctg tgactagggt aggagctaac 63120
atacattgat tatggcaagc aaattgtttc tagtcactgt acatttcaaa ctatactgtt 63180
catggaagat atacttgtat atgtgcaaaa gcaagaccta tgcttccatc cataccatga 63240
ccacatggtg cattttaaa aacgaccctt ctccagtgct ttctcccttg catgttattt 63300
ttctttggga gaaatgtctg tgctatttgc cattgtctct ccatttccta gcagagttcc 63360
tagtacagtt ctgttctaat tttcatctga aatattctta tttatctatt tatttttaat 63420
tttactttaa gttctgggat acatgtgtga cgttcccctc tctgtatcca tgtgttctca 63480
tcgttcaact cccacttatg agtragaaca tgtggcgttt ggttttctat tcctgtgtta 63540
gtttgctgag aatgatggct tccagcttca tccatgtcct tgtaaaagac atgaacttgt 63600
tccttttag ggctgcgtag tattccatgg tgcatatatg ctacattttc tttatccagt 63660
ctatcattga taggcatttg ggttggttcc aagtctttgc tattataaat agtgctacaa 63720
taaacataca tgtgcatatg tctttatttt ttgaaagaca ttacagtgtt tccactttgg 63780
atttaccttc actctggaaa ttatgcaaag aatttagact aaactctggc aagtttagag 63840
atggtagcgt gtgtctggat gccacagaat agcaagttta ggggtcaaag attctccttt 63900
cagtgctttg taaagcacac agtaggttct tcatttaggc aaatgaagaa gatatttttg 63960
attaataata atgataaacc atatgttata ttttgtagca ttttataaat ttcagagcat 64020
tatataaatt ctagttgtta ctattaggtt cctttatgag gacaataggg caggcactat 64080
tataatctct tatgaataaa caaaaacttc aaagagaagc gtgacttgtt tgaggttgta 64140
tagtagagat agggcttaat ttgtcttcta gttccaagtc tggtgattgc tcttcatgga 64200
gggctttatt tacagaagga gaaagtccta tcttgtacaa gttaagagac caccagaggc 64260
ctgtaccacc agccaaaagt ctgtgtcttt atcccttatt tacaagtaga tgaaaatgag 64320
tgctttattg caaatgcagt gggactaaag gaactgctac tttggggaaa ataaaagtca 64380
gctgaaacag aatgtttgca gccaagacta aagtcactaa tacaaccggc tcacaacttt 64440
gccaatgaac cttctggcaa aaacctggca ggatacgaat atgtaagtag ctgctgtaaa 64500
agggaacgaa gcagaggaaa tgagctttgt aagttattat atctgggcag gaatttttaa 64560
tcaagttttt ttttatttaa aaaaatttaa gtacaaatag ttggtgaaat aatgattcac 64620
taaggaaaga aaaccaaatt tgkcttactg tttctggaat catacaagtc atgaaccctt 64680
cagggcacac tgtgacctaa aatgaatcac atgcatgtaa gggattttgc agtgaggcat 64740
tctttcctat ttccctctac cttgtttatt tatagctaag tttcatttat ggagcagtgt 64800
aaaaaaaaaa acctcagaaa tcagaggaaa tgtagaaaag aaacttctta ttcttttgtt 64860
agtgctttga tctggtcaca gtcagatata tacaagaagg aaatgaatgg cctcgatcaa 64920
agtccttaga aaatgctagt ataggggatg ggttgcagga gtgatcccat tttgttttcc 64980
ttctttgttt aaagctcttg tggaaagtgg gaaagggaac tgccagtcac cgagcaccag 65040
ccaccacytt acccactttt cacgtcaatg ctgcaaggtg ggtatgagga ccagctctgt 65100
tttacagaga ttgtaaagat tatcaagatg taagagtagg ggagccagga ttttaaccta 65160
ggtctaaacc atatgcctgt gctcttaaaa gattttgctt taggaataga aacgtataac 65220
ttatttttgt ttaaaggtta cttagctatt ttattatttt tacatattat ygtctaaacc 65280
ttttttagta tggaaggttt tttttaacat atacaaaaga agcatgaagt gtatagtgaa 65340
ccccttttgta tgcatcactc aattacatca atgatgaact cataactaat attgttttat 65400
ttattctctt tattctcccc attattttga agtatttctt agacattgta taattccacc 65460
tgtaaatatt tcagtattta tctctaaaat ataaggactg aaacataatc ataatatcat 65520
tatcacacct aaaaattaaa caactcttct ttaaaataat cagatattga gtcagttttt 65580
aaaattcccc aatcatcttg ttatttttta tagtttgatt atttaaatca aagtccaaat 65640
aaaatcttta tgttcaagtt agttgatatg tctcataagc ctttcaattt rtggggtttc 65700
cttctatttc tgttctttac ccctwgcaat ttacttgtta aaaaaaaaaa acccaggtca 65760
cttgtcctgg agtttcccac agtctggctt gtgttcattg tgtcccctga tgtcctttaa 65820
cacattctct gtcctctgta tttcttggca attagtagct agacctggag cagggtttct 65880
cgaccttcac actaatgaca tttgggaccg gacagttctt tcttgtgcat tgtagaatgt 65940
ctaacagtat ccctggcctc tatccactag atgtctgtag cattgcccag tcgtgacaat 66000
ccaaaatgtc tctggasgtt gtcaaatgtc ctccaggagc caaatcatcc agttgagaac 66060
cactgattta ggggactgaa caggtgcaag gattttcttg gtggggaaac aagggaaggc 66120
aagagtactt tttatataaa tctgtgtatt ttcattagga gacacaggat agctagctgt 66180
ctgtgatgtg agtagccatt gatgatcatt gctgaaatcc atttagtcat agcagtactt 66240

agttatttta aatgttgcat tagatatata acagctgtta ttagttgctt taaattagaa 66300
tgttttcatg tgatcaaaga ttaaatgagg cttagccaga aatcatcttc atgagacatg 66360
acactttatt atttctgcag tgacgatgca tggaaatcat tacttgtgga caaacttaga 66420
attagcctgt gaatggggct tttgtttttc tatttctcag aaatagaatg gcctatagga 66480
atgaatatat taggtacctg gaaaccacct aaaaatagta atggatgttg gaaaagctcc 66540
aaagaaggrc tcaattcttc cctctaatat tcaaaaggat tagggagctt gatgttgtag 66600
tttgtagccc tgcctgtcat tccagacccc taggttgtag ttcataccct ttcaagcttc 66660
taaaatcaag acactgagct ccaagacaga gtaccttgtg tccattccgg gcattccttt 66720
acagaacaaa gagtggtgtg taagagtcct ctcagggagg caggcaggga gagaggaggt 66780
gagagaatgt tcgagatggt gaggaagggg aggatattag ggtctcaaca aaaagattat 66840
ttttgagata aatgtggtat agtatgagag attcttattg cgtttggtct ttttatctgc 66900
ttcatcttta tatgcataag gtattggtgg ttattttacc cttttagaaa aatttttgaa 66960
tatatatata ttaaaacctg tgaaacaggt aaaagctcat tttccccctt agttctttta 67020
ttattcaatc tggtcatctg taaaatggma tctcatatta aacagcttgt caattaactt 67080
ttttttttt ttaaggaaca gagagattca aaactgcggt ccattttact tctaatggga 67140
ttagcatcaa ggaaaaacca ctcatgcagg gtctaagata aacatcagaa caatgcagca 67200
attataggtc attcaattaa tatattgayg tgactttcag ttgctcaaaa atagtacagt 67260
ttttttctgt taagtgaaaa gattattttg ctttttcaag caccatatta gaatgatttt 67320
ggtgtgaata aaactattgc taattatcgt tggtttgcag cacttctctt ttgttactta 67380
ggaatgccaa agaaagggta aaatccctgt tacaatgaag gctttcttgc tggtaatcag 67440
cagtayttgg tctgcctgca actggggctg ctttgtccca gaagttttat ttctattgac 67500
tttctgctct ttagaattta aacatttttc tttatatctt taactgctga aactccagct 67560
gagggaacag tgggagggga ataaaaagat ggttaaagtc atttygtgga ctgtgagggt 67620
gcatgaagaa catgttcttc aaactcagtt ccacatttaa gctgcccagc gagccttgcc 67680
cttgctattc tctctctccc tgaagccaga aagaagaagc aggcgactct ccaaaggacc 67740
ccatcttacc tgtcacatca cagatgtacc tttttagcat tctcacaatt gagataggat 67800
tcagagccct gaaacctgga ggaaggaaag aaaactctct tttatttagt ttccatcata 67860
caaggatgtt ataaatatcc cccatcttta aaaagatcct aagatccctc ttagctgttg 67920
ccaattactc tgctcccttt tacaacagag tttcctagca ttaacgttaa tggctgtttc 67980
cgtttaccct cgtcctgttt ctttctttaa aaaaattttt tttacatatg tgatatatcc 68040
aactgattgt ccttttttta gaacccactg aaaatagtcc ttcatcttca ccaatctcct 68100
gaaaatattc tttcaatgct accartgact gccattatgc taagcctaat ggttcttgtt 68160
caaatatcac ttctcagaga gctactcccc acagttactc tttacctttt acccagctct 68220
atttttgcaa gttttttttc ccattgtgac atttacttta atagctgtaa tttcactctc 68280
ccaaatagaa tgtctgttcc atgagaaatg ggattttatt tcattcttta gtaccttgca 68340
cactataggt gtgcaataat tatttttgta tggattgatt aataaaatgc tgtgggaatt 68400
gctacttcac ttgtaatttt gtttaccttt taatttaatt cttagcacag tatctatgaa 68460
gtcagatttc aataaataca tgttgagcac aagagaattc taattaagaa gaaggcagca 68520
ctctgtagaa taactggttt ctaggatatt gacattcatc cagcaatgat ttgctgatga 68580
gtattcaaat tatttggggc tacatttcca gcagggaggc tgagccacac catttctagt 68640
gattggaaag tggctactct tataatgctg gggtgcagct agttttcctg tctctttgat 68700
tagattttgt cttttgttct gcccaggtgg gtccctggga ataactacta aagtatgaaa 68760
ccatggtgtt gtctggcttt caatgaaaac atgtagccyc gtgccactaa acatgatgta 68820
cattataaac atttgtttac cccttagaag gcatcttact tctttgtact attccttgga 68880
gcatttgatg cacatttttc catcttgttg ctcggtcact tttgtaatag agcttgtgtg 68940
agtttttttt ttttttaagg aatttagaac tatrtcagtt tttatctcct ttgcagtttt 69000
tggtgatagc tctgttatgg gaagaaggca gtgctgtgga tctggactcc ttggagcaac 69060
cctctcaggc acatttctag ttgaggtcta agattaggtc actgtggata gagaccagca 69120
aggaatctca ggcttaagac ccagttagta caaagggagt gagctaagga aaactagata 69180
acttagttta tttctctttt tcctttggct tcctgaaagc cacccagact aaacttgatg 69240
ttagttcaat tctacaagtc ctcgggatga ccatattttc tttctctttc caaggtgctg 69300
aatttctttc tttctttctt tctctttctt tctttctttc tttctttctt tctttctttc 69360
tttctttctt tctttctttc yttctttctt tctttccttc tttctttctt ctttctgaat 69420
ttctttttta ataaatctgg ttttatataa ctttttattg aaagcttctt caaattactt 69480
ttggactggg gaaggatatg cttctctgtt tttttccttg tatattactg cattccctar 69540
gagctagtcc atgatggcag tcactttagg gacttgaaat tcaccaggaa tgggggtttg 69600
gggagtcgtg gtggtacctt catgagacta actttatggc ctgtttttttg gtatygactc 69660
tcctgtttgt cctggtactc cttctggaaa gttatttttc ctgtgtaggt ttcctagaat 69720
tcctagawtw tatcatattg aagtactttg ttaactatgc cataagttgt gggaaactag 69780
agttggcctc acttttccct tcttcctaat gtggatggga aactgactgg cagaaagaaa 69840
atcttccccc cttcctcttg ggtttcttct ttttcttttc ataatctctt ttaagaattt 69900
tctattacca tttcattcaa tttctttctt ctttaatttt tcgcttcttc ctgttactta 69960
ctctgcagcc tataagtggt agatgtatct gtggtagtgg ttagtaacct gggttatgga 70020
gccaggttga ttggatttga attctggctc tccaacttta ccagttatgt gacctttttc 70080
aaattcctta acctcttaat gctcaggttc ttactctata aaatgggagt catcatagta 70140

```
tttacttcat gaagttgtta tgaagatgaa atgagtttat acatattgag tactttgaca 70200
catgtctggc acatagtttt taatacatgt tattgatgat gatgatgatg atgatgatga 70260
tgattgcttg tttaactttg tgggtagcgc ttgaagtaag tgctkktggc caaactggta 70320
gattctttct ggcaaatcat tacattgact ggattaatct gtcttggagc cagaggaaat 70380
aacataaagt aacttataaa ggatgactct aggaccttga aaagtcccag gtgtctgggc 70440
tggacttgta tcggtaattt cttgtgtgtg tgtgtgtgtg tgtgtttccc aatcttggct 70500
taagtttcct aacctacttt taagattcct tcttcataat aatggttttt tctatgttgt 70560
cctcagccat gttgtcaaat tgtgagaata aaacatgtct gcagtcttcc tgtcaagata 70620
ataatgaaca gtgccttata tttgtatctt actctgctta aaatgatttc cattctaaga 70680
ggtctacaag rtcttcaaac tacatttcta caccctcctc cctgattatg taaacagaac 70740
tatagcatag aaatttcttg cttcaaacca aatcattaac agtgaaaaaa tataaaaact 70800
cttgtctgca taattttggg gcagctccca attatggggg aacaaatctg aacatgtatc 70860
atttgggatt gggagaaagt aaagaaaggg gaagcaagga gtggtatgag gaaggatatt 70920
ctcacctttt tgtgttagaa aaaaccttaa aggtctgagg cttaatttat agctacttgt 70980
tgatctttcc atyaaaacca aattcagaag gaagagtttc cttggtgttc ttatatatgg 71040
tctcctctca tattgcactt taccctatac ttaaattctt gcaggacatt atagccacat 71100
gatggatttg ctctgtggga agaaggttag acttaggctt gccaagcaaa tgaaccaaaa 71160
aataagactt tagatatctc ccagttggaa gctcaaagga ttgtgaatta ttgttttctg 71220
gagtagattg aaactcatta acatctttag caatggtagt agaatccatt catttctttc 71280
tttgctcagt gttracagtt tggacctgtt gtctctgtgt gggtctccaa agagggaaaa 71340
ccattcagaa acagattttc aggtattttc agtatttggt ggagttaggg agctctgtgc 71400
aatctttcct atgagtatac atcccaggtt aactatgcac craagagatc aaggtgtgca 71460
ggggttgaga ggggtcctct gctgattgag agtgattctt tatcagtgtg gatggagaca 71520
agaaagctgt gtgttcctca ttccaaaagt caaactgctg acctctggcc atcacaatac 71580
cctccctgat gatatcaagc tgggcttctt gtttgttggg tggggaatgg gccttgtcag 71640
taaacttgta gtcatgtcag tggttacagt tttaatcttt ccccttcaa ttttctggca 71700
ctggctctca aaaagcagga tgaagaaaac gagagatcca tccagcacac ttattccaga 71760
ttctttatat ttataattat caccttaaat gaagtagcca ccgttcaagc ccagattaat 71820
tttcctccag acagatagct tatctattgc aaagagctgg gttttctacg agtttttctt 71880
ctgcttgctg ctgctcttaa aaggctagat aacacattga ctctaggagc tatctggctc 71940
acaggggcaa aggaattgct tgctgacctc acctggtctt ttgcatctct tgaagggaga 72000
attaataaac atcacttgaa gggagagttg tgtgactcat ttgaaggcac atttgtaagg 72060
catatcatct cagcgaggaa agacgcaata actctaggca ctggctcact tttggactat 72120
taaaaaacaa aataaaattc agaaaaaatt ttaaatttta accagctatt taaaaatgcc 72180
ttccatttta acatatgatt gactatatgt aactctggca attgagatat ttaaggacac 72240
ttaataaact agctttgaac ctctggagat gagaagagtt aggcttattc ctttactata 72300
ccaaaaaaaa gatcattgga gagtccattt ttttaaaaag tgcaagttgt taacatggca 72360
caagtttagt acagtttcag cacagaattt tgtgcatggc ttctgcttga aaagacttgg 72420
gactatccaa agaattatct tcaatatatt tatatctcta taaaatctca aattgggttc 72480
ttaagtgcaa aattgagact caaagtcaat taagacatac cttttccttg gttaaaaaga 72540
aatcagaaga tgacctgata atcactacaa aaataatctt tcatgaagaa gatggtcaga 72600
ccaaggaaga tatcacattt gtgaaaagga gggtattcaa aggccataaa aggcagaact 72660
tcaaaatatt ttaaaaagcc raatgaacta aaatgttcac ctgtgataaa taatagcaac 72720
attgaacatt tctcaagcac agagagtaat gtcccacccc tgtactaagt gtgcacagtg 72780
agaaatgtcc caccctgta ctaattgttg gggattctaa aatgagtaag acaggatcct 72840
tgatctcagg gagtttcatt atgtcatggc ggaaagagat caaccatcca cagaataaag 72900
cctccagtaa gaagtcatga gagacaggtg gtccaagtct ggcaagtaga gaggagggac 72960
agatagcacg ttattcctgt aagggacttc ctgattttca actgtgacct agaaaaccag 73020
gtccagtgag tagcagtgag gtggtcatat gtacataacg tggcaacaac aatttgtgct 73080
ttgaaagcac attatgcttt tcaacatgct ttaccagaca tggtcttttc aggccgctct 73140
accctgtgca gtaggttatc caaatgtgca gatagggaag tagcaacatg gagaggacat 73200
gaagcttgag tcacagtaaa tagctgctta gtggtacctc tgggccgcca gggctcctga 73260
actctaggcc tgctttcttt ctgcaacccg ccagtggaag aaatggcctt tctttttcc 73320
aagcttgtgc agtggtactt tagtttcctg ggatgttatc tgtatcatgt aaaagaatgt 73380
ttgattttga actaaagtta aattctttct cattcttcat cttttggctc aaaagtyact 73440
tcttcagggg atacttttct gggcccccaa atctctctgc tatgcagtct cacagtcctc 73500
tgtactttcc acattagcac ttatcccagt ttgtaattta ccatttgtgt cttatttgat 73560
taatgtctgt ctcccatgtc cagccttact ctccatgaag ccagggagca tayttctttt 73620
gtgtatcaat atatgcattt agtgacttgc atatagtaat cactcaataa atgtttgctg 73680
aaggaaattt aaggtttgtt tactgtttcc ttttcctttt ttttttttt ttttttaca 73740
atagagtacc caacatgtga gcagcttact tgtgacaatg gggcctgcta taacaccagt 73800
cagaagtgtg attggaaagt tgattgcagg gactcctcag atgaaatcaa ctgcagtaag 73860
tattgtgcac aagatgtgca gttgtgtgct gaagctggtt tatactggtt tgagagagcc 73920
aatatgtaca tctcttccca agttcaggtt cagtgaattc atgttggtag tttgaagtca 73980
gccgttggta ggagtattta cacactggaa atcggcaaac actacaaacc agggcctttt 74040
```

```
tgttcctgga taactggttc ttaaacagtt accagcacac cactgcttaa taagaatccc 74100
tttttaaact ggagatgctc ttcctttgag attaaatggc tacaatggag ttaacttctc 74160
tcttttcttt cccttcttaa ctttctgttg cagctgagat atgcttgcac aatgagtttt 74220
catgtggcaa tggagagtgt atccctcgtg cttatgtctg tgaccatgac aatgattgcc 74280
aagacggcag tgaygaacat gcttgcagta cggtgatttc tttatgctgg gtcatgttgt 74340
tgggagtgtt ttgttttgtt tcggttttgt tttgttttat ccccccgctc csccaccaat 74400
gtacctcttt tttcaaggag aagagtcact acgtttgatg gcagatggaa tcagacggtc 74460
actagggggt cttggcacaa gcctttgtgg tgttgctcga cctgggctcc tttattttcc 74520
aaggatctgt gtagatgtaa agggctggtg atggacagtt tgccttcttt ccttaggctc 74580
caggggtaca ggatatattg tatcactgga ttctcaaatg acccatacct ctgacaacct 74640
tgatagtaga atgagagaag tgtttttaag ggaaaggaag ttcctaggag tggctctaac 74700
tctcctcttt actttgaaat ttctgctgca ttaaagttgg agggtcagga aagtttcttt 74760
ttcttcgttt tctttttttt ggagatggag ttttgctttg ttgcctgggc tggagtacag 74820
tggcgcgatc tcggcttact gccacttccg cctcctgggt tcaagcagtt ctcctgcttc 74880
agcctcccga atagctggga tcacaggcat gcaccaccat gtctggctaa ttttgtgttt 74940
ttagtagaga tggggtttca ccgtgttggc caggctggtc tcgaactcct gatctcaagt 75000
gatccgcccg cctcggcctc ccaaagtgct ggtattatgg gtatgagcca ccacgcccag 75060
cctgaaagtt tcagtgtggt ataggtggct ttcttgcctc cacttcttca ckctgacctt 75120
gcttttatgt ccatgctgtt gcctgcaatg caaatgacct ctcttattgt tgccacctct 75180
ccacttatgt tttttggaaa gagtaaagtt agaagactct gtgaaagagt tttactatgt 75240
tcagtaagtt ggcagctttg cgtggtgatt tatttactag aatgtatgat ttccctccac 75300
acctcttttg attggttggt acccatgcct tagggtgttg ttaaatattt tcratatcac 75360
cctaattttc aatgagccat gcctgacttc ctttctggaa cctgggctta tttcagtgac 75420
agagaattaa agagaatgtg acatcatgga atggtcgact cagaatcatt tggtcataga 75480
ttagcaatta cggagcttgt agtaaagtat gagaacgttg gatgttgtca tgtctgcagc 75540
atctttgtct gcattttctg ttctgtgcca acgcattgca aaccatcttg tttttaattt 75600
ttttttttt ttttttttga racagggtct cactctgtca cccaggctgg agtgcagtgg 75660
tgcgatcttg gctcactgca actccacaca cccccaccag gctcatgcca tcctcccacc 75720
tcagcctcct gagtagctga gactacagac atgtaccacc atgcttggct atttattttt 75780
atttttcgta tttttggtag agatgaggtc tcaccatgtt gcccaggctg atctaatttt 75840
taatcttgaa aaacagaaac cggcacctga gttcatttcc tggacccaaa gctgctgkta 75900
tcttcttctt tctctctctt ttttwtcctc ctttttaaaa atttttgtca agatgtctaa 75960
gggattaaat tgatatagaa atttcawttt ctaggagtac tgcttaggca gtgaggtgag 76020
agcactttca gtttttcccg gtgatttgtg tctttggagt gcagctgttg ctttattcca 76080
gactatccga cctgcggtgg ttaccagttc acttgcccca gtggccgatg catttatcaa 76140
aactgggttt gtgatggaga agatgactgt aaagataatg gagatgaaga tggatgtggt 76200
aaggagggga agagaytcct actgaaaagc attttcttca agtgttttcc agcgcttgtt 76260
ttttctcctt tccttttag aaattttgtg tgacaagcaa gcctcaggat tggctggagt 76320
tgaaggggtt gtttaggaac ttagtgggtg gggaagacgg aggtgactgc gctaacttct 76380
cctaagaaga ttcagaacac aaatacagat taaattataa tcctctccct tctatcttta 76440
aggcaaaata ggtaggacag tctctgtctc ttctataccc cagtctgact ttctccctgt 76500
aagactgcct gttttaaata gatttaaaac tatataaaac taataggctg gggaaggaaa 76560
gaaaataggg aaaatgtcat ttgtcttaga ccttacaatc tttaaaaatg actttgaacc 76620
ttggtaacag ttcagcttat ttttttgttt tggttttgta aattctgatt cccaaatgag 76680
tcactgacac tcagtggtga aagagaggcc accttgggaa cacgtgggtt ggagctgggg 76740
attggtaagt gtaggagaag ctactatcca gggaagtgct taaagattcc gtgagaagga 76800
aattgccagt gatattcacc cttttatgtt gctgatattg acccttttat gttgctgata 76860
tcatcagcag tacctccaac aatttagcag ttactaatac ccatacccta cagcaagtta 76920
cctgcaccat tccaatccca ggtatgataa gggaaatgct tgttaaaact atgttttatg 76980
tttttatgtt ccagaaagtg gtttttctac atttgggtta tggtttttct tatactgttg 77040
acatttcact aaataaacaa agcaaatcaa aaagcccaac cacaaattca agtaattctg 77100
gacctaactt gatggcccta attctataat tcatgattta aataactaca tcttttctta 77160
ggggatcatg aatttagttt gtcgataatt gaggcccata tctgcttctt cctcttataa 77220
ccctactggg ggctgcctht tccaggaaaa gtggagtaat tccattatgc ctctccttag 77280
aatctcagta aaagactagt ggtagagtta gaaatcacta acttattgta aaatgtagat 77340
catttataga tttctcttgt tcaacttgct ctrcatcctc tgtaaaccac tgattaacaa 77400
agagctggct gtacctcccc tatggcctgt aactctctct ttttcccccc acagaaagcs 77460
gtcctcatga tgttcataaa tgttccccaa gagaatggtc ttgcccagag tcgggacgat 77520
gcatctccat ttataaagtt tgtgatggga ttttagattg cccaggaaga gaagatgaaa 77580
acaacactag taccggaaaa tactgtagtg agtatagaca tttacctggg tagctttcag 77640
ataaagatat ttctgttttc tagaacagac gttcaaatac agtgtatctg ttggcrtttg 77700
cataacaaag caccccaaga cttagtggca taaactgaga aacgtgtctt atttctcaca 77760
gttctgtggg ttggctaggt agttcctctg gcctgtatca gctcactcac acgtcaggat 77820
gttgcagtaa aagcttgggc tagcctagcc ttgttgaccc agaggctgaa agagcaaatc 77880
ctagggctca agtactttca aggttctact tatgccaagt ttgctcaagt cttattgtcc 77940
```

aaagcaagac acttggccaa acccagagtg gatggaagaa atagactcca tctattgatg 78000
ggaagagcct aacaattttt tagcaactcc ccgttcctaa tccctaacrc acacacaggg 78060
aggattgttt caatggcaat tttgatgacc ttaaagatgt tctggagatt ttattacctg 78120
gcttatactt atggaaaaag gccttgtctg gctgtactaa aaaaaaaaaa aaaaaaaaaa 78180
aaaaaaaagc ttctggttcc tgggttatgt accttgagtt actctccaat ggcaaaactg 78240
agttggccat gcacagtgtt gttcgattat gtcttgtgtg accacattca tttatgagga 78300
aactgactgg aactagggat ttttttctct ctttttgggg gctgtagaat attcacccca 78360
ccaacaaccc mtcaactctg tggacagctg atggtcctgt aaggaaatgc catttaaaac 78420
cttgatttca tcaataatat actctaacta aatttgtgat tgcctagaag tgcccatgta 78480
actgcaaccc caaggttatt ttttgtttcc tgacaaaaat tgtacataat atttaaacag 78540
gcagagacct ctatggcatt tttttctcta tttcatttgg gagcccattt aaaaaagctt 78600
aaaaattaat aagagatatg tagtcacagt atgaaagttg gaaaataaaa attaaccaaa 78660
agaaaaaaat ataatcacct gaaatcccat ctcttgaagc cagccacagt taatatttct 78720
agggcttatt cttgctccag tcacttggga gttcttagcc ctttttacta tgtagacaca 78780
aagatagacc catgcatgac ctgatttttt tttcataaat aagactttta atgacttata 78840
cttgcacata gttataactt taaaaaggag ctttttyttt tcttttgttt ccactcaagg 78900
cagcctcttg ttctgtcacc caggctagag tgcagtggtg cagtcatagc tcactgcagc 78960
ctccatcttt tgggctcaag tgatcctcct gccttggcct cccaaagtgc tgagattaca 79020
gttgtgagcc actgtgcctg gctaatgctt ttatttttaa ttttttgtga atatgaggtg 79080
tagctacatt acccaggctg gtcttgatct cctggcttca agcaatcttc ctgtctcagt 79140
tgaactttta ttgcaaagtt ttgcagtaag ctttgaaggg tgacagattt ttctgtacat 79200
ctacttcatg cttactgagc tgctactcat ggaaaaagaa gctattagat taatcagtct 79260
tgtccagagg tcaccattca tttaacaaag ttcttttctt cgtttaggta tgactctgtg 79320
ctctgccttg aactgccagt accagtgcca tgagacgccg tatggaggag cgtgtttttg 79380
tcccccaggt tatatcatca accacaatga cagccgtacc tgtgttggta agtgatgggg 79440
ggcggcggct acttgtcttt cattacagta cactgatggg tgccctgatc tctgacatct 79500
aggaggttgc acttgtggag agtcgtcatg gtctgtyata acaaagagca acccagacct 79560
cacagaaaac ctggcaaata gggaatttta actctgagaa ggtttggtgt ggtgtacaag 79620
gcaaaagaat ggttctgtca tgagcgagtt gactagctay ctggaaccta tccattactt 79680
gatgagggcr gtagtccttt tctgttttct tttcaagtat ttggcatcag gattggtgca 79740
gccatactgg ttattgaata ctgaactact tccatgaggt tggtagatag ctgctgcctg 79800
agcccagcaa gcaccgctac cttgctcccc tggcctcttc tccaggatgc acaagcatcc 79860
ccaggatccc acaactaaag gttgttacct gacacagcag aggatcacca ggtcattgct 79920
caggtgacta cactggtggg ccagtgcctt tgctgggctg gctactcatt ccactgattg 79980
tgacatccac ttggaactat cattcaagat gagcagattc tttatcatgg tgcttccaga 80040
tggtggctgg cattaaacta gacaccagta caccaactat ttcctcatat ctctcctctc 80100
tgacttcaga aatgatttct cccaatgaga tttttgattt tgatgccagc tttatatctc 80160
actgtgatta ggaygggggcc ttatgatggg agaattagac ttgaccaact atcatcagtt 80220
tttgttttct cagtgagttt ttggtgctct gatctttttt ccttctatct gatttttgat 80280
acatgaacaa caaacatact agcaggaagt gatcacagag ggagtttaaa gaaaactatt 80340
tttactgctg ttgggaaaag gcatctggaa ggcaattgaa actattcatt aaaatttggt 80400
agtcatctat ggggctccaa aatgattcag aattttccca ggatatttat attcttttga 80460
tattccttag aaatgtgagg tattctttag ggcttttggg atagcaacaa acatgaaatg 80520
tgtaagaaat gcttctagaa aagtatttct tctgaaatta ttattttaat attattaaaa 80580
tattaaaatt ttaatattaa aatattaaaa ttttaatatt ttagaactat ttggtaacat 80640
ttggaaaaaa ttattgaata tagataaacc taatgcagtt attcagtctt tagtctcagc 80700
tcattgcttc caacataatt atactttgtc aaatacagct aatcttaaca actactcata 80760
gccagaaaag cctttctttt tttctttatt attattatta ttattattct tcagcggaag 80820
tgctagcaaa cagaaaaatg tattgatacc agaaataaac tctggtttgc aaattaaact 80880
tgaaattctt gagaaagtct gctcctcagc gttactgaaa actacaatcg ttgggctcac 80940
ttacctacca tatgccaaaa aaaattagat ttttatatcc agtaaagcaa tccatttgag 81000
cttttccttg tgttcatagt gggtaactgt aggttcttaa tatcaggacc acgtcccaaa 81060
gttgcccatc taattgctcc tcttaagtaa ctatattcaa caaggtactt taagatcaag 81120
tgacttaagt gaactctgga ataatttaag aaggccccca aatttctaat cattttaaaa 81180
cattttayaa ataaaagtta tgatctgcaa ctggacttaa ataagattgc aggacacatt 81240
ttgtgtttta ttgttatcat taccattata ttgggaatgc attcaagtaa tttacagata 81300
cttttcacac gaatgccctt attggttagg tggtgacctg actctgggag ccctgcctgg 81360
atttcaggca gccctgcgca aaggggcagc ctcacttctg ctcagagtgg ggctcgtctg 81420
tgggtgtgag gccactcctg tgtctttagc aaatgtcagg ctcctttkcc cccctcactg 81480
ctacccagct gccaatccca ttcccagcct tttagttctt taggcatttt ccttttctct 81540
tagtagaaaa gaagttccaa tagaaatacc agaagccaca ttctcagtat tacatcagct 81600
tttctctctt tttcctttat caactcccaa agaggmgttg gggctgagct gtcttacagt 81660
tgaaacttga taggccatga agkcctttca ggaaaagtga tttgttcttt cagaatcgct 81720
aattcagtct tgtgatgccc cacaagctgt tctcagtttt ttgttccacs ctagagccca 81780
gataacacat tttccatatt ttccaacata taagtctgtg gtgagccttg ggttgtattt 81840

ccaaatgtct agggttttct aaatgtcaga gattcaggcc acttcaattt tcaatagcct 81900
ctcacaaagc gaaaggctgt cataacaatg ttcttgtttt ataaaatttt gcatttaacc 81960
tactagtgaa tgtaaggcag aatattgcag tattatgtgt gcacaggata atttcaggat 82020
cagagaagat accacaatta ataacacatt ggaagtagtg tgttctaata ccggggcact 82080
aattttaagt tccacaacag acatcttctt tcattcccgc cagcgcgttt ctgggacttt 82140
agtacagaca acctcatttg gagataatct caaaagtcta catttgaggg cctttgtgaa 82200
tatgaggcct cctgccacct gcagagacct tttctgtgac ctttgctgtc cttcaagaat 82260
gtgtcatttg cctctgagtt ttgaggctgg gttaacattt atttcacatt tgtttcaaag 82320
aagactgtat ttttctctct ttatagagaa ctctttaaat acatgacgtt aggaaaccag 82380
ttacacttgt ttcagctgag ctgaattttt aggggaattg ttgctttggt ttgctctctc 82440
aagcatttca tttcaacaaa tactctctgt atggctataa ccctctgcat ggctgacgca 82500
ttacacaggc ttcaggtgtt ggaaacctat gcaacattta ttatcttaga catggctccc 82560
cagtgaatac ctcggtggta atcaagaata acattgaata atcctgacac gaaatcttgt 82620
gtctttctac cattcatctg cctctggtag tsttgacctg gcagtggaag ctctgaggca 82680
tgctgaagca gtttactggg ctcattgttt ctgattgaca ggacatgctg tttgttgaca 82740
gaatgacatc gtggtgcaga gtgagggcag ggaggtcatt cagcatggtg gggtttcaca 82800
cagccagatg gatcagaggg trgccaaggg ggkctcagtt aaaaaggggt ttttgagtca 82860
ttttcacagc agtatttgtt ggtgggagga gacaaagaat aaaaaggaaa gaaaaataga 82920
taaaggtatt ggagtgagag ggggattgta aagtagtgtt ttagtgtttt gtgtggtttc 82980
cactatcttt tctactctca cgaaaaccct caattctact tttatttttc ttgtcttcac 83040
tctggctgct gatggatgtt aattaacctt catattcctc tatagtgatc caaggataca 83100
atcttattgt cacaaaagtg acagcaattt tatacactca ttcaaatcct gtttttttgtg 83160
atagggtctc actgtcgccc aggctggagt gcagtggcat tatcacgctc actgcagcct 83220
cccacttcag cctcccgaat agctgggact acaggcacgt gcctccatgc ctggctaatt 83280
ttttttttt ttttttaat tcttagtaca cataaaccct tgccatattg cccaggctag 83340
tctcaaaccc ttggactcaa gcaatcctcc caccttaccc tcccaaagtg ctgggattat 83400
aggcgtgagc cactgtgcct ggcccactca ttcaaatctt taaaccactt gtagtgcagg 83460
tgataggaag ggcatttgtg ctagagaatt cctagttatg acttctccac ctttggtttc 83520
cttctgtttg acatcagaac ttctgcttag agtgactcca gatccttaga cgtggtctca 83580
tggatcttgc attcaaaatg aagttatgac attctggggg tttgagggag aatgtcctgt 83640
actttttttc ctgctgaggc aaagccttag gtggagcttt ctcagggctg agttaagggg 83700
acagaaggga ttcatcagtg agggcatttc acaccctcat gtggcatttc acttggtagt 83760
gtccagatcg gattgggttt tttttcctct ggttagtcac ggtccttgga aagaaagata 83820
tgctggctca tgttgttatg tttaatctgc agggaaaatg ggatcattag aagagccttc 83880
ttggggctgg atgcggtggc ttacgcctgc agtcccatca ctttgggagg ccaaggcaag 83940
ctgcttactt gagatcagga gtttgagacc agcctggcca acatggggaa atgccgtctc 84000
tactaaaaat acaaaaatat tagccaggtg tggtggcgca cacctgtagt tccagctact 84060
cggtaggctg aggtggaagg atcrcttgaa cccgggaggc ggaggttgca gtgagccgag 84120
actgtgccac tgcactccag cctgggcaac agactgtgac tccatctcaa aaaaaaaaaa 84180
aaaaaaaaaa aaragaaaaa aaagaaaaag aaaagaaaag agaagaaact tggccttttg 84240
gtgggttatg gaatggtggg ccacccagca ggaatggttg aacccaattc acaactctga 84300
cagttgctgc aaatgtaatc agatcataga aatctggaga attctagact tgggagtgca 84360
gtggtttcag aaattataat ctacttgaga acttcctgaa accagagggt gtgggaactc 84420
tattgttata gtttgtatag gtcatcctcc cagggaagcg aggagggtga aggatgatgg 84480
agagtggacg tggacttgga aagtcagatg taccaatttc tgcacccctg aagccttata 84540
gtctttaaga aagactcttc taatattttg ttgtgttctc ccctccatat tctattgttt 84600
atgtcaatta tattggaact atttttamac agtagaactg ggacttctct ggtaatgaac 84660
agagctctgt catgtaaggg acttcaatga acacttacta aatgagtgaa taataagtta 84720
accaataagt agaggagaag acatttttga tgtcttgaaa ataagttcaa tttaattttg 84780
gttataattt tttgacatca gaggaaagac agctgggtaa atagaccttt ccaagtactt 84840
tattgcagtc atagatttgt ttcttcctga ggggctgtct ataggcaggt cttactttat 84900
tcagaaatag tgctgtccaa tagaactttc tgcagtgatg taaatgtgta tcttcactct 84960
gtcatattgt aaccactagt catatgtggc tattgagcac ttgaaatgtg gcaagtgact 85020
aggaaagcaa attattamtt ttattttatt ttaattaatc taaagataca tttagatagc 85080
cacagggggt tagtggctrc catgttggaa agcatagtat tgaagggaaa catttacacc 85140
aaaatttata tatttgtaga ctaacattaa taaatgaaat gcagtaccat agggctatga 85200
attcaggaag tgttgtgcat tttctgtaaa gttatccttc atgtaggttt aaaaaatgat 85260
gtaaatgttc tttttcctta catgaagatg gttgttataa attctcagaa cctgtgccta 85320
aytccagagg gtgtttattt agacatgggc aacaccacat tcttggccat cttatctagg 85380
atttttgtca gagagtgctt aataaatgct gataaccttg actacaaatg tgtattttcc 85440
atatggcaga gtttgatgat tgccagatat ggggaatttg tgaccagaag tgtgaaagcc 85500
gacctggccg tcacctgtgc cactgtgaag aagggtatat cttggagcgt ggacagtatt 85560
gcaaagctaa tgattcctgt gagtaaatta tggacacctg tgtctctgaa cagtraacag 85620
attctaatag cttctttcct tccttctgat gacaacagaa ttatcagcat ttttgttgtt 85680
ggcagggctt tatcattaca aatcagggat ggctcctact gcctagaaaa attggtcaac 85740

attaatttca tactttgatt attaaggacc aatttgtcga ytaatggtga ccattattaa 85800
tatttttaa ttgattgatt gtttactttg cctaggctat catgtcaccc acctttaatt 85860
gtggaataaa tgctatgcct acatttgatt ggcttggaca tttaactttt aattaattac 85920
ctaccacaaa agtaggcgac aactatctac agaaataatt ttcacagtgt tcttgcaaaa 85980
tttagggata tttccaaatg gacatgctaa atttggatta acaatttttt gaatgcacta 86040
actctgggta atttgttgga atcartgtaa gagtatgaaa agtagagagt agtacagagt 86100
agtagagaaa agtcatggag aaaatctgca aaaaatagat gagggctcca aagcattttg 86160
tcgctgttga tttctccgga cgaaggtctc aatataaact cctattttcc aatagttatt 86220
taacacttga ttttgaagtg tctttggtgt cttctgaaac ttaactgctc ccatgactga 86280
agaatggccc attttctact tgtttttgtg tagaaatacc tgatttgctg tgtagtaact 86340
tttaggttca gcggattttt aacaattcaa tgtgtttatt tttgcatagg taacatattt 86400
atatgttcac aaattttaaa ttataagaag atatgtagtg aaatgccttc ctccrtaact 86460
attcccctct gcatggtttt caccttctct ttcctatgag taattgccgt ttctttattt 86520
tagttctaga gatttttaa tgaataaaca agaacataca aatatagata tttaactgta 86580
tttacatatc tatatatggt agtaaactat atgcacagtt ctgcatcttg tgaatgtact 86640
gaagatattt tccagagctt tccatttcag cacatgaagt tatttcttaa ttattttatt 86700
tatttattta tttatttta tttatttatt tttgagaatg agtctcgctc tgttgcccag 86760
gctggagtgc agtggcgcca tcttggctca ctgcaacctc cgcctcccgg gttcaggcaa 86820
ttctctgcct cagcctcccg agtagctggg actacaggct tctgccacca cacccagcta 86880
atttttgtat ttttagtaga gacggggttt catcatgtta gccaggatgg tcttgatctc 86940
ctgacctcat aatttacctg ccttggcctc ccaaagtgct gggattacag gcatgaacca 87000
ccgcatccgg ccttatttat ttatttttga gatggagtct tgctcttgtt gcccaggctg 87060
gagtgcaatg gcaagatctt gcctcactgc aatctccgcc tctcgggttc aagcgattct 87120
cctgcctcag cctcctgagt agctgagatt acaggccccc gccaccatgc ccagctaatt 87180
tttgtatttt tggtagaaac agggtttccc catgttggcc aggctgatct cgaactcctg 87240
acttcaggtg atctgcctac ctcagtccct caaagtgctg ggattacagg tgtgagccac 87300
tgcgcctggc cttaattatt tttttataat ggcataatat tccttctttt atgttcataa 87360
tttgtttaac tagtcctcta ctgatcaatt tttatatcat tccttatctt ttgctattgc 87420
caataagact gcaattaata ccttgttcat atatcatttt gcatacctgs gagtaaacag 87480
acagaacaga tttggaacca ccattaccat ctttttcaga gtgatttcct ggtaatcttt 87540
aaaatgtctt ctgtgtttaa caaaatctaa agttgcacat ggggctaagg tgcccatacc 87600
atcaaggagt ctcgaaaata tctgagaaat actctcctca gtgtcattga aagtgcattg 87660
gactagcatc cagaatgctt gaattcttac caaattcttc ctaacttact gagattttgg 87720
acgcttcatt aagccttttt gtgcctcaat ttgcccttct gtaaaatgga yagaatgcta 87780
gctatctgtc tgcctcagag gtttatgtta aaatcaggta agacaaccta gaagatagca 87840
tttgaaaaag cagaaagcat atcatttgta agctacttca ccatccttgc tcatctgaag 87900
gagtggtgat gccttccttc ttcgcattta gttggcgagg cctccattat cttctccaat 87960
ggtcgggatt tgttaattgg tgatattcat ggaaggagct tccggatcct agtggagtct 88020
cagaatcgtg gagtggccgt gggtgtggct ttccactatc acctgcaaag agtttttgg 88080
acagacaccg tgcaaaataa ggtaaataga aatttcagta gctgaatgga accctgagca 88140
caaagtgttg atagcttttc actyttagag ggagtagagg ggaaagttcc tttgttttct 88200
aacaaaaaag gcccttgaga tattttatgt taatcagcac cttttccatg ctatactatt 88260
acatstgacc tattaaacaa agcagtctat tatatggatt agccttgagc aacttttaat 88320
tttattcgaa gtggagtcca ggagcctaat taaaagaaat agtagacatt ctttcaaaac 88380
tggatagata tttggtagta atttttgaaa tttgatcatt taaaatgtaa aaagcacact 88440
gcttttctgg atgataaaaa tcagattttt acctgcatct tctaaatgga actgtaattc 88500
gggatcgagt aacaaatatt gacggtattt tgtttaatgg cccaaatttt gtttcactgt 88560
cttatttgga aagtgtgatg ggtttaattt catcttggag taatgcaatg gagatttttg 88620
aaacataaat ttcagaaact cttaaagagt tatggaattt tatttatttc ttcttacatt 88680
ttattatacc attaatacga ttctcattta tttaaatgat aacttgcatg aaatttctga 88740
aaattgagaa tttagatttt tagcacttct gatttgatta kagctaaaaa aawtcaaaac 88800
aamccacgta gttagtgatg ctgaagaaat ayaataattt tggtttttct ttcaggtttt 88860
ttcagttgac attaatggtt taaatatcca agaggttctc aatgtttctg ttgaaacccc 88920
agagaacctg gctgtggact gggttaataa taaaatctat ctagtggaaa ccaaggtcaa 88980
ccgcatagat atggtaaatt tggatggaag ctatcgggtt acccttataa ctgaaaactt 89040
ggggcatcct agaggaattg ccgtggaccc aactgttggg taagtgatgt gaaaacatat 89100
tgattcctgt atttttagaa ttttctctct ccctctatac ackgaacatc tactggatta 89160
atcaaaggct cattctgatt tcttttaggc tgtatactct agaagccatg tctattttrt 89220
gcccttattt atagaagctt taagagagtt tattaaatat aatcctattt gaggacatgt 89280
tacccaaaca cacctagtgg tgtactaaaa atacttgttg ttttggggct atgaatttta 89340
ttcttagtgt ttgccacgtt ttcctagcta agagattgga ttttgtgttc taactcaatc 89400
taataatatt attacaacta aacatcactt atgcttcatt attattaaga tgattactct 89460
aacatgaatt agctgtaaag atttttaaag atggaggttg gaactattcc tttcagaact 89520
ttcttgatac aggctgggat tgagatatca atgctaatat ctcattacaa gttgttcagt 89580
ctgaatcaat ccagcaacac cgataatgct tttcttcagg tttaaattta aatttcccaa 89640

tcttcacatt tgagaagtgt tataggagac ttagctttct cctagaattt cacaattggg 89700
tcttaggacc cttggataag ctttaggcta ttttagtctt tgtgaatgat gattattcag 89760
ttctacttca ttatatcagc tatccttcct tgaaaatgac ggaaatgttc tctgtgcctc 89820
agaatggaaa actgaggagc aaaatggctt gatagcttct tttaaaaggt atttgtaagt 89880
tttcctgggt gtaaaaaaga gaagcaaagg acaaataaag gaaacagagg agaaagttca 89940
gaaggtgaat atgaattttt ttttttgag acaggttctt gctctgttgc ccaggctgga 90000
gtgcagcagc acaatcacag crtgcygcag acttgaactt ctgggctcaa gcaatcctcc 90060
cacctcagct tcctgagtag ctgagactat gggcaagtgc catcatgccc agctaatctt 90120
ttaatttttg tagagatggg gtcttgccat gttgcccagg ctggtcttga aacatgggcc 90180
tcaagcaatc cttctatgtt ggcctcccaa agtgctagga ccacaggcat gaaccactgt 90240
gcctggctgg ctgaatatga acttttagac tgccatatta gtgcatcata atagttgcta 90300
tttggaactg ttgatgctcc tgactgaccc ccacagtctc tttaaaaaaa aaaaacaact 90360
taatttccct gttgttttat actgtggttc tctaatcagc tggataaaat ttccattgat 90420
ccaaacacac tgttaaaaaa aattcccagg ttaacttgta aaataccaga ttctttcatc 90480
ttctgttttt cttttgtagt tatttatttt tctcagattg ggagagcctt tctggggaac 90540
ctaagctgga aagggcattc atggatggca gcaaccgtaa agacttggtg aaaacaaagc 90600
tgggatggcc tgctggggta actctggata tgatatcgaa gcgtgtttac tgggttgact 90660
ctcggtttga ttacattgaa actgtaactt atgatggaat tcaaaggtaa gaagtatttt 90720
ttatggctta tggctttata agttgcaggg aaagtgcata aaatggctgs agagaaatat 90780
caaaggacca gaattaaaat attgctttgt tggtggacat gatagcttta atgacctttg 90840
tactgacatt tgcatgaagt gacctgctct attttgttaa cttttcttgt gtcccataac 90900
acaagaggta aacgctcatt aaatataacc tccagcattt gttctttgat ttctcctctc 90960
caactcttcc cctagtccca catgatgcac attattttca ttcactcctg agttcatttg 91020
tgctttgttt ctcaagatca ctttcccttt taattttcta accttccccc aataaataca 91080
tgttttatta ggtatttgat gttgcctact gggaattaat tggattttac tctgctctta 91140
tatatttcaa atttcaagga gaaattcttt gtattgtatt tttacctggt atacaaagat 91200
acttaaacrg caatatttga atgtagaata tggctttctt ttttttttt ttttttgaga 91260
tggagtctca ctctgtcacc caggctgaag tgcagtgatg cratctcggt tcactgcaaa 91320
ctccacctcc caagttcaag tgattctcct gcttcaacct ccccagtagc taggattaca 91380
agcatacacc accatgcctg gcaatttttg tatttttagt agagataaaa tttcaccgtg 91440
tttcccaggc tggtcccaaa ctcctaacct caagttattc gcctgcctcr gcctcccaaa 91500
gtattgggat tacagatgtg agccactaca cctggctgaa tatggcatat tttttttcat 91560
ctttttactc tgattagagc taactayaac ttaatgtaaa aaaaattatt ttagatcctc 91620
tccttttggt attttcaaaa attgggtaaa acatgttctt caaattttga cccaaaatat 91680
tattctttgt ggattcagca aataggctgg ttaacttaat ttttcccaat gacttgattt 91740
tattgttttc tcaatgaaag caatattata gttttgtttc ctcttgtatt tccattttgt 91800
aaggataata tcacagtttg ccattggatt atatatcctt gggacaatct ctgcttggtt 91860
aaatgaagta ttgkgtatta atatggtgac ttcctatcac tgaaactggc ttccataagg 91920
agaatatgaa taaatttttat gaaaaaatta gctaacccaa taagtcacat aaaataattg 91980
tgaaattgct taaatttttt ctctttggga tgttttagca ttatattata tagtctaact 92040
tttgctgaag taaaaaaaag taaagcataa aagataaaaa tcaatggaat ttcaaaaaga 92100
tttgagtggt ttgctggctg tgaagaaaca tcaaagaaat attaaagctc acaagtacag 92160
ctgaaatcat aaagtcattg cctctcgctt tgccagcagg tggcattcag ggttttggaa 92220
tttgctaact gagagagaaa ctattctcta atcttaatgt accatgtcat tatagaatgt 92280
ttcaaagtgt gcactaacct gccaccttag gtttctttgt ttactcccct ttagtgtgtt 92340
tcccagcttt aatatcttca agtcttttct tagagctcta ttgtcctttt tagttttcag 92400
gggatgctaa gatttttctt tgaggtcttt gtattacgcc aaaataaaga aaataagagt 92460
tttcccatat caaccgtcct ctgcctcact ctgttcatga gtctaactga atcattgttt 92520
atggagacat agtcacgggg ggcgttgttg atttcctctc ttcgcttagt gcctaatttt 92580
acttctgttt tcttcccagt taagtggctt tgggcctcca ttacaagtat gatcagttga 92640
tagttccatc aagcagatgc ataagagtgg tagtggcatt gcttcttgct ttccttacag 92700
tgacatcagg aacagaygtg ggcgtttkct ggggcttgaa ccctaccact cactgtcctg 92760
ctccctaatt gctaggaaat gctcaatggt gmagtgggaa atagttggca aaggcatctt 92820
ttcccagact tccaaagtct tggtatactc tttcacttat ggtattcaaa atgctatttc 92880
acatcttagc cttttagatg tggggcaacc taaaaggaat gaagaacaaa aggggaaaca 92940
gtaaattcca aaaaagtcta ggacaagcta aaggattgac tgggactgga atgtaagtct 93000
caagggtctt ttccaagaga caacatgaaa atccttctat catatgtaga tggaaatatg 93060
tatacatcta aaatgtatct tttctatcta ttccgtattt gtgacaagaa attatttagc 93120
ttttcaggca tttaattgaa ctaactacag ctttaattat aataaagcaa aactaacaaa 93180
ttgtatgata tatatgtgtc ttttataaca ggaagactgt agttcatgga ggctccctca 93240
ttcctcatcc ctttggagta agcttatttg aaggtcaggt gttctttaca gattggacaa 93300
agatggccgt gctgaaggca aacaagttca cagagaccaa cccacaagtg tactaccagg 93360
cttccctgag gccctatgga gtgactgttt accattccct cagacagccc tatggtaagc 93420
ctcagagcag tggtaaccat gcttggtacc ggacttggtg gaaaggtttt ctcaaagctt 93480
tgaaagttaa taatgagggg tcttatgtga tttgggtggc attctcaagt atatgaaggg 93540

ttacccagag tgttaaactc tctgaaactg gttctgcagg ttaggagcat tctgaagaaa 93600
ctgatgtatt tcacagttaa atgccaaatc tagagggaat ttagagattt atttaacaga 93660
tgtttattag cacctgcaaa gatgcttggg ggtatagcag ctcacaaacc aaaccaaaat 93720
acctatcctc attctactgg gaaagacatc tatttcaaac ttctaatatt acagttaagg 93780
aaacaggtcc catagaagaa aatgacatgt ctaagtgtcc attttcggta gcatcagagc 93840
cattttttc ttcttctctg ttgcatatgt atggcacctg ttctttggtt ctgattaatc 93900
tgtcataggc caactgggtt tggtgtctct ctggctggtc acttatttta aaaaaagaaa 93960
tattttgatt cagacactgc ttagtcttct cctgttattt taccacgtga ttttttcttt 94020
ttatttttc tgagatggga tttccactat gttggccaga cttttctgga actccgggct 94080
tcaagcgatc ctcctgcccc ggcttcccaa agtgttggga ttacaggtgt aagccactgc 94140
acctggccta tcataagctt tgtttatgtt tccaggttat agcttgagct ttgataagtc 94200
tatcaggact gtatatagct cttttctgta tttgcttgtg gatcaaagaa aaagaaacat 94260
aaactacact acgttggtag aaagcttaat attggtgagc aataatttag aggaaaacag 94320
atttgctcta aaactcatgt taagtgatgg atctatttag gatgaagaaa gactgcaaag 94380
taatgaggtt aacttaacaa aagcccaacc actagaamtg acacattcag atgaatctcc 94440
ttcaatgtca tcatcctggg aaagtataaa cttgtctaaa aatagatatt ttatctgaaa 94500
acatttttgg aaatatctgt tttgaatagt ttttacactc aattcacaac taaactcaca 94560
cctgccctca cattagatcc attagatcaa tgatcaatgt gatcactcaa attactattt 94620
tcattatttg gctcagaatg acatctgcct attgtttccc caaatcaatc cacctgagaa 94680
gataaagaga atattttaaa gaataagtca aaggctaaaa agacaatttt gaaagcagat 94740
ataaaatttc tagctgtggc agtgctcttc ctaaggtcac tactttgaga gtggcttttg 94800
gaagtataaa ctggtttgtg ttgcagacat ttaaggtttt ggaatcagat ctggctttga 94860
atcctagtca agctgtttag ctgctgaata atgttgggca agttatttaa ctgtttagat 94920
tcttggtttc tcctctgtaa aattggagga ctaatactta cctcttagag ctattggtta 94980
agttggttta cttacaaagt aagcatccag tgagtaatat ttattatatc ctacaaatgg 95040
caaaaaagca gtgaagtgtg ggttttcttt tgacaattat ttgtaatcat ggaggatagc 95100
agacatactc tgacataatt attggggaga aagttgtagg agtcctttct ttttttttgc 95160
caccgtctgt tggagagtgg atgggagagc agcagtgaaa ttgggagggt tagtgtagcc 95220
agatgtggat gtatccagta gtaaccagta gtaatgtttt caacacgttg ctaatccatt 95280
actctatttc acctataggt gaaaagggct agaagtggct tcaygtcttg gataattaca 95340
catttctaat tgcaatttaa ccctgtgcat ttttccttcc agctaccaat ccgtgtaaag 95400
ataacaatgg ggrctgtgag caggtctgtg tyctcagcca cagaacagat aatgatggtt 95460
tgggtttccg ttgcaagtgc acattcggct tccaactgga tacagatgag cgccactgca 95520
ttggtaagaa gtctgttttg gacrttgttg gcaggtgaca caggtgtatg tgtgtccaaa 95580
cctctaacta gactaactgc tactcttgaa ctggaccagc tccctgtcta acttcttgac 95640
tgcaaataag ctttctgtag cccacagggc atcttccttg gtaggcacca cttctactat 95700
acacagaact atgtttgaaa atgtaaattt ctgtcttttg ggattttgct ttaatcccac 95760
atctaaggtt ttcttgggtt cccttccccc tttgtttcct gaagcctttt tctcctatta 95820
actatgatct tgaaattcca tatggttgaa ctttgagctc ttttctatgc tatgtatacc 95880
ttttccactt tagatgttag ccttaacttt gatgggaagt actgtacttc tccccacttt 95940
gacttctcct agaccaccac gtatgcccct ttcaaccagg taatcacatc tgaatcttat 96000
ctggcttatt ttttctctct gtattccaaa gtaaactcct gagcattggg gtggctcagt 96060
tactcacaca gtttttcacc tttcagttca aactttcttg tatctgcctc catattcctg 96120
atttcattct taccttgaag gtttcctttc ttcctctttg gtttcctaca catctattca 96180
cacttaagcc atcgcctggg ccccagctaa tgatgaaatg cactcctaca atatttgttt 96240
ttcttatttt cacttctaca wttctccttt ctgtgcctgt gacaaattct tgctctccag 96300
atgttgcggt ttctagcgtc gtatataaat tatcttattc taacccagac acatttgtta 96360
acttcttagg tagttttaga ttcagaaaaa tcaccctcat taaaaacaac atgtatttct 96420
aactattata tcaatagtgc gttgtctaat aattttgctt ttaaattccg ttactgcgat 96480
ttttatcttt gtcttgggca tacctccttc atcttcttga ctccctggca tcctgtcaca 96540
gtctcctctt tgctgttaaa catcacttct tcttacctat ttcctttatc cctccccttc 96600
cttccctgct ttcactcctt tayatcttta tatttctgat tgctgttaat tatcttggta 96660
tctactgtaa ggttcttggt gtagatctct atgcagaagt taaaccaact tgaggattgt 96720
tacggaatta ctatagagtt cagctctgta tgatttttaa acaaaagatt gatggcacag 96780
gtgagaaagg tttctgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgcatg ttttgcctgt 96840
ttattgtaat gatacttata acttgataat taaaactcag tatctaattt ttaagcagtc 96900
ctttttattt tatttattta tactatttta ctttaagttc tagggtacat gtgcacaatg 96960
tgcaggtttg ttacatatgt atacatgtgc catgttggtg tgctgcaccc gttaactcgt 97020
cattacatta gatgtatctc ctattttata aattaagcat atggatatca tttttcatat 97080
aaatacattt taaggataca tttcttagga agaaggaaga ttctaatact tgtatctccc 97140
tcatagttgc ttatctttttt ttcttccctg tattatttct aactatgctt tccaaaaatt 97200
tatttttaca tttatttcag aattatattt tataatttaa agtttgctct gtggatgcat 97260
ttatctggaa tttgggagga gagaaaagaa ccatgctgtg actgactgtg ctgtgttatt 97320
cttcctacag ctgttcagaa tttcctcatt ttttcatccc aagttgctat tcgtgggatc 97380
ccgttcacct tgtctaccca ggaagatgtc atggttccag tttcggggaa tccttctttc 97440

tttgtcggga ttgattttga cgcccaggac agcactatct ttttttcaga tatgtcaaaa 97500
cacatgattt ttaagcaaaa gattgatggc acaggtgaga aaggtttgtg tgtgtgtgtg 97560
tgtgtgtatg cgtgttttgc ctgtttattg taatgatact tacaacttga taattaaaac 97620
tcagtatcta atttttaagc agtcwtattt atttatttat ttatttattt atttatttat 97680
ttatttatac tattttactt taagttctag ggtacatgtg cacaacgtgc aggtttgtta 97740
catatgtata catgtgccat gttggtgtgc tgcaccygtt aactcgtcat ttatgttagg 97800
tatatctcct aatgctatcc ctccccctcc ccccacccca cgacaggccc tggcgtgtga 97860
tgttccccat cctgtgtcca tgtgtgctca ttgttcaatt cccacctgtg agtgagaaca 97920
tgtggtgttt ggttttctgt ccttgcaata gtttgctgag aatgttggtt tccagcttca 97980
tccatgtccc tgtaaagaac atgaactcat ccttttttat ggctgcatag tattccatgg 98040
tgcatatgta acacattttc ttaatccagt ctatcattga tgaacatttg ggttggttcc 98100
aagtttttgc tattgtgaat agtgccgcaa taaacatacg tgagcatgtg tctttatagc 98160
agcatgattt ataatccttt gggtatatgc ccagtaatgg gatggctggg tcaaatgtta 98220
tttctagttc tagatccctg aggaatctcc acactgtctt ccacaatggt tgaactagtt 98280
tacagtccct ccaacagtgt aaaagtgttc ctatatctcc acatcctctc cagcacctgt 98340
tgtttcctga ctttttaatg atcgccattc taactggtgt gagatggtat ctcattgtga 98400
ttttgatttg catttctctg atggctagtg atgatgagca ttttttcttg tgtctgttgc 98460
ctccataaat gtcttctttt gagaagtgtc tgttcatatc cttcacccac tttttgatgg 98520
ggttgtttga ttttttcttg taaatttgtt taagttcttt gtagattctg gatattagcc 98580
ctttgtaaga tgggtagatt gtaaaaattt tctcctattc tgtaggttgc ctgttcactc 98640
tgatggtagt ttgttttgct gtgcagaagc tctttagtct aattagatcc catttgtcaa 98700
ttttggcttt tgttgccatt gcttttggtg ttgcagtcat gaagtccttg cccacaccta 98760
tggcctgaat ggtattgtct aggttttctt ctaagggttc ttatggcttt aggtctaaca 98820
tttaaatctt taatccatct tgaattgatt tttgtataag gtgtaaggaa gggatccagt 98880
ttcagctttc tamatatggc tagccagttt tcccagtacc atttattaaa tagggaatcc 98940
tttccccatt tcttgttttt gtcaggtttg tcaaagatca gatggttgta gatgtgtgat 99000
atcattwctg aggactctat tctgttccat tggtctatat ctctgttttg gtaccagtac 99060
catgctgttt tggttactgt agccttgtag tatagcttga agtcaggtag tgtgatgcct 99120
tcagctttgt tcttttggct taggattgtc ttggcaatgc aggctctttt ttggttccat 99180
atgaacttta aagtagtttt ttccaattct gtgaagaaag tcattggtag cttgatgggg 99240
atggcattga atctataaat caccttgggc agtatggcca tttccacaat attgattctt 99300
cctatccatg agcatggatt gttcttccat ttgtttgtgt cctcttttat tttgctgagc 99360
agtggtttgt agttctcctt gaagaggtcc ttcacatccc ttgtaagttg gattcctagg 99420
tattttattc tctttgaagc aattgtgaat gggagttcac tcatgatttg gctctctgtt 99480
tgtctgttat tggtgtatag gaatgcttgt gatttttgca cattgatttt gtatcctgag 99540
cctttgctga agttgcttat cagcttaagg agatattggg ctgagatgat ggggttttct 99600
aaatatacag tcatatcatc tgcaaacagg gacaatttga cttcctcttt tcctaattga 99660
atacccttta tttccttctc ctgactaatt gccctggcca gaacttccaa cactatgctg 99720
agtaggagtg gcgagagagg gcatccctgc cttgtgccag ttttcaaagg gaatgcttcc 99780
agtttttgtc cattcagtat gatattggct gtgggtttgt cataaatagc tgttattatt 99840
ttgagataca tcccatcaat acctagttta ttgatttagc atgaagtgct gttgaatttt 99900
gtcaaaggcc ttttctgcat ctattgagat aatcatgtgg tttttgtctt tggttctgtt 99960
tatatgctgg attacgttta ttgatttgtg tatgctgaac cagcattgca tcacagggat 100020
gaagcccact tgatcatggt ggataagctt tttgatgtga tcctggattc ggtttgccag 100080
tattttattg aggatttttg catcaatgtt catcagggat attggtctaa aattctcttt 100140
ttttgttgtg tctctgccag gctttggtat cagaatgatg ttggcctcat aaaatgaatt 100200
agggatgatt ccctcttttt gctttgattg gaatagtttc agaaggaatg gaaccagctc 100260
ctctttgtac ctctggtaga attcggctgt gaatccgtct ggtcctggac atttttggg 100320
ttggtaggct attaattatt gcctcaattt cagaacctgt tattggacta ttcagggatt 100380
cagcttcttc ctggtttagt cttgggaggg tgtatgtgtc caggaattta tctatttctt 100440
ctagattttc tagtttattt gcatagaggt atttacagta ttctctgatg gtagtttgta 100500
tttctttggg atgggtggtg atatcccctt tatcattttt tattgtgtct agttgattct 100560
tctctctttt cttctttatt agtcttgcta gcggtctatc aattttgttc atttttttcaa 100620
aaaaccagct cctggattca ttgatttttt gaagggtttt ttgtgtctct atctccttca 100680
gttctgctat gatcttagtt atttcttgcc ttccgttagc ttttgaatgt gtttgctctc 100740
gcttctctag ttcttttaat tgtgatgtta gggtgtcagt tttagatctc tactgctttc 100800
tcctgtgggc atttagtgct ataaatttcc ttctacaccc tacttcaaat gtgtcccaga 100860
gattctggtg tgttgtgtct ttgstctcat tggtttcaca gaacgtcttt atttctgcct 100920
tcatttcgtt gyttacccag tagtcattca ggagcacgtt gttcagtttc cgtgtagttg 100980
agtggttttg agtgagtttc tggatcctga gttctaattt gattgccttg tggtctgaga 101040
gacagtttgt tataatttct gttcttttac atttgctgag gagtgcttta cttccaacta 101100
tgtggtcaat tttggaataa gtgcratgtg gtgctgagag gaatgtatay tctgttgatt 101160
tggggtggat agttatgtaa gcagagattt tactaagctt cctaaatagt tttagattga 101220
gaaaataaat ttattgcttt tttatggatt aaggtaaaac aaacaccttt cctttatttt 101280
agaaacacgt tatttttggg aaccgagacg ggaggattgc ttgaggccgg gagtttgaga 101340

ccagcctgag caacatagtg agattccact tgtaccaaaa aaagaaaaaa attagccaga 101400
tgtggtggca tgtacctgta gtccccacta cttgggaggc tgcaatggaa ggattgtttg 101460
agcccaggag atccaggttg cagygagcta tgaccatacc actgcactcc agcttgggca 101520
acagagtgca accctatctc ggaaaaaaaa aaaaaaaaaa ggttacaaac gtgtgtgtat 101580
tttaacaatg accaatgtta acataaaaga aatgtcacgt gtatgagagc cattaacaga 101640
ttaattgact agacactgtt tttcatactc aagcagccag attgattaaa ggggaagaca 101700
tctcttcagg gatgctggac tatgtaaatg ccaagggttt ggtttgtaat agtaataaaa 101760
tttgtaagca atataacata ccaactaaga gagccagctt aggagctaca ctgcctggtt 101820
ccaaattcca gcttcccaca tttcctagct ttgtaacttt ggggaagtta ctcaatttcc 101880
ttttgcctca attttctagt ctgaaaaata tgcggttcat atattgctca taaggttgtt 101940
gagagaattt ttggctaatg catgtaaaca cctagagtaa tggctagaaa atagtaaata 102000
ttcagtaaat gttggatatc attwtatctg ttatcaatat aaaaccatat tgcccaccct 102060
cccctgcccc taatccagac ctgctctggg gagggaacag ctcttttgac tatttcttct 102120
tttgtttgtc tccatgtttc taaatgcttt gtttatactt ctatttcttg atttatcatt 102180
tttgatattt acttccttgt tctaggtgag cgttttgctt tcttacatca ttcttctctc 102240
ccagcttctg acttccctcc ccccattctc cttaaaaagc tagattataa tttttggtta 102300
aattaatcat atgtgtttat attattaaca taatataaat ataaatattg ttcactgctc 102360
agccaattag tattctagga tgacatttct tgacaatttt tgacaattgc cccattttca 102420
tttgcttagt ttttaaatat aacaatcatg tattttcccc aaatgctcta atagctctat 102480
caaatgcctg tacaaagaca gaaaacaatc tacaattttt tttttctttc tggagacccc 102540
tatcctgtgt tccaattggg acttgttttt ctctggcctg gtgcacagac ttctctttgc 102600
cactcccctg tgctggaact tctgtttgtg gcaggccatt tatttctttt tctagattta 102660
tttcctcatt ttgctgaaac amgttacatg atagcttcct gagaaacata agtaggtggc 102720
atatattttg agtctttgaa tgtctgtgag tgttttattt tgctctccat cttgactgtt 102780
tggstgggta caggttgcaa gttaatttaa acctggaatt tgaagacatt gctctagtga 102840
cgtctaatat ctagtgttga gtccagtgcc attctgagta ccatttctat ggatatgact 102900
ttgatatgga tatggatatg acattaaaaa ttaatcttcc tctgtttcca ttttctctgg 102960
attccttttc cttttgattt cttttcaact ttcttctttt tgatggaagc tttttccaag 103020
tgtctgagtt gctagtttgg tattaagggt gaggttataa aacctgaccc aaaagtctgt 103080
acatgtggat aggccttgtc agctggtrag cttcaggcag gaaggtggct tggttgccag 103140
attgctcccc aaggcaacat tagtgagtct tttctggaga tggtcaattt ctccttcata 103200
gatgcctcca ttttccttcr tgaggtaagg ggaagatgtg gggagatggt kgtctgttct 103260
gggggtgatt aatttctcct ccatagatgc cttcattctc cttcttggag taaggggaag 103320
atgtgggaag atggtggtct gttctggggg tgattaattt ctccttcata gatgccttca 103380
ttctccttct tggggtaagg ggaagatgtg gggagatggt ggtctgttct gggagtgggc 103440
agaggaaagg gagctgaggg cgccctttca gtattcctat aatcctcctg tactcagttc 103500
cacatccatc tcagttctgt gttgaggact gtgccttgaa cccatagcca ttctgcttca 103560
gctcctccag agaaaatctg tggtccctta gaggagatag aggagtggcg tgacactcag 103620
gatctgggag ggacctaggc attggattgc tccttatctt gctttatctg agccccttag 103680
ttcctcgccc ctgcctttgt taggacctgg tgcctctgag tgtgagtgca ctgaggcttc 103740
tgcatatgtg ggtgtgtctc tcttctgttg acacttagtt tgtagcattt tccccttctt 103800
aactgagtta tcactcctcc aataccttac ttttcaaaca tttgttggaa ttactcatct 103860
gctgttattt tactgtcttt taagtagaat ttcggaggaa gaggagataa acatgtttgg 103920
tttgtcaatc tgctattttg aatgagaaat tatctttttt gaggacttag aatcaggccc 103980
actgagcttg gagcactgca gtcgagctta gttctcagga aaaggtagta ttgggtttct 104040
agctgcatgc aggccaagtc tcccacaggc acctccacag gtcagcttcc ttctgttttg 104100
ttgatctgga attctcatag tatttttggt aaacttcaag ttcgtatgct gagcaaccta 104160
ccttttttwa attttttttat ttttatttat ttatttatta ttatacttta artttaggg 104220
tacatgtgta caatgtgcag gttagttaca tatgtataca tgtgccatgc tggtgcgctg 104280
cacccactaa ctcgtcatct agcattagtt atatctccca atgctatccc tcctcccgcg 104340
ccaccccaca acagtcccca gagtgtgatg ttccccttcc tgtgtccatg tgttctcatt 104400
gttcaattcc cacctatgag tgagaatatg cagtgtttgg ttttttgttc ttgtgatagt 104460
ttgctgagaa tgatgatttc caatttcatc catgtcccta caaaggacat gaactcatca 104520
ttttttatgg ctgcatagta ttccatggca tatatgtgcc acattttctt aatccagtct 104580
atcattgttg gacatttggg ttggttccaa gtctttgcta ttgtgaatag tgccgcaata 104640
aacatacgtg tgcatgtgtc tttatagcag catgatttat agtcctctgg gtatataccc 104700
agtaatgcga tggctgggtc aaatggtatg tctagttcta gatccctgag gaatcgccac 104760
actgacttcc acaatggttg aactagttta cagtcccacc aacagtgtaa aagtgttcct 104820
atttctccac atcctctcca gcacctgttg tttcctgact ttttaatgat tgccattcta 104880
actggtgtga ratggtatct cattgtggtt ttgatttgca tttctctgat ggccagtgat 104940
ggtgagcatt ttttcrtgtg ttttttggct gcataaatgt cttcttttga gaagtgtctg 105000
ttcatatcct ttgcccactt tttgatgggg ttgtttgttt ttttcttgta aatttgtttg 105060
agttcattgt agattctgga tattagccct ttgtcagatg agtaggttgy gaatattttc 105120
tcccattttg tgggttgcct gttcactgtg atggtagttt cttttgctgt gcagaagctc 105180
tttagtttaa ttagatccca tttgtcaatt ttggcttttg ttgccattgc ttttggtgtt 105240

ttagacatga agtctttgcc catgcctatg tcctgaatgg taatgcctag gttttcttct 105300
agggttttta tggttttagg tctaatattt aagtctttaa rccatcttga attgatattt 105360
gtataaggtg taaggaaggg atccagtttc agctttctac atatggctag ccagttttcc 105420
cagcaccatt tattaaatag ggaatccttt ccccattgct ttttttctca ggtttgtcaa 105480
agatcagata gttgtagata yacggcgtta tttctgaggg ctctgttctg ttccattggt 105540
ctatatctgt gttttggtac cagtaccatg ctgttttgct tactatagcc ttgtaggata 105600
gtttgaagtc aggtagtgtg atgcctccag ctttgttctt ttggcttagg attgacttgg 105660
cratgcgggc tctttttgg ttccatatga rctttaaagt agtttttcc aattctgtga 105720
agaaagtcat tggtagcttg atggggatgg cattgaatct ataaattacc ttgggcagta 105780
tggccatttt cacgatattg attcttccta cccatgagca tggaatgttc ttccatttgt 105840
ttgtatcctc ttttatttca ttgagcagtg gtttgtagtt cttcttgaag aggtccttca 105900
catcccttgt aagttggatt cctaggtatt ttattctctt tgaagcaatt gtgaatggga 105960
gttcactcat gatttggctc tctgtttgtc tgttattggt gtataagaat gcttgtgatt 106020
tttgtacatt gattttgtat cctgagactt tgctgaagtt gcttatcagc ttaaggagat 106080
tttgggctga gacaatggga ttttctagat atacaatcat gtcgtctgca aacagggaca 106140
atttgacttc ctcttttcct aattgaatac cctttatttc cttctcctgc ctaattggcc 106200
tggccagaat ttccaacact atgttgaata ggagcggtga gagagggcat ccctgtcttg 106260
tgccagtttt caaagggaat gcttccagtt tttgcccatt cagtatgata ttggctgtgg 106320
gtttgtcata gatagctctt attattttga gatatgcccc atcaatacct agtttattga 106380
gagtttttag catgaagggt tgttgacttt tgtcaaaggc cttttctgca tctattgaga 106440
taatcatgtg gtttttgtct ttggytctgt ttatatgctg gattacattt attgatttgc 106500
gtatattgaa ccagccttgc atcccaggga tgaagcccac ttgatcatgg tggataagct 106560
ttttgatgtg ctgctggatt cggtttgcca gtattttatt gaggatcttt gcatcaatgt 106620
tcatcaagga tattggtcta aaatgctctg ttttggttgt gtctctgcct ggctttggta 106680
tcaggatgat gctggcctca taaaatgagt tagggaggat tccctctttt tctattgatt 106740
ggaatcattt cagaaggaat ggtaccagtt cctccttgta cctctggtag aattcggctg 106800
tgaatccatc tggtcctgga ctctttttgg caacctacct tttaaaatat tcctcatagt 106860
cagtggttaa actctgtatg ctttgttgag ggaggcatta cattgttctt ttttttttt 106920
ttgaatgagt acacagtata tgcaggaaat gagttgtcag aaatcaaatt agctaatgtg 106980
gtggtgtggt gtagtgccag atacttggga ggatcacttg aggtcaggtg tttgaggctg 107040
cagtgggcta tgactgtgcc actgcactcc agcctaggta agacctgtct ctaaagaaaa 107100
agaaaaagaa atcatattaa aagtcaggat tagctgaatg aarccctcag gagaactccc 107160
tccttcaatg ataccttctt ttttccaaat tctctttttc tactgacttt tccctatcat 107220
cagatatgct caagtttctc ccatcctaaa aaatatgcaa cttacccttc actccatgtt 107280
cctctttagt gataacccct tctctgcatt tcatggtcaa gtttcttgaa aggttgtttt 107340
gcactttcct atcccttctt ccacatttct cactgattac tcacctcttg caatctgccc 107400
accaggtggc tgacacccct ctcatcctgg tcacctctaa tccctttctt gctaaattaa 107460
ataatgccta tcagtcctgt atttggtact tcagccatct tctctcaaat attctttctt 107520
ccatgacagc atactcctgg atttccttct atttcttgat catttttttt ttttctagtg 107580
taccctggag atcttttctt tttctcctgt tctataaaaa actgtaaatc tgttgttcaa 107640
cattggtcct cctctctctg aataatttca caccttteet gcctttgatt actatctatg 107700
tagcaactat aaataattat ggggagactt ttataatagt gcatttactg agtgtttttc 107760
ctcctaaact ggggaatgag ggaaagacca agcaagcctt tctgtaggtc atgataaaaa 107820
tctctatgca agttctctct ctgaggttca gacccatagt gccagctgcc ttttggatac 107880
gtcacctgga tatcctacaa tcacctctaa accaacatgt ctaagtggat gcttcatcca 107940
acttctcaca ggccttagag gaagggcatg accactcacc ccttccttgg tgccccatcc 108000
ccacctggtg gtcatcatga acatctccct ctcttttagc ctctatcatt aactcattaa 108060
cctccagcca cactcctaga acatgtagag ttttcagtct ctgtgtctgt caaccacccc 108120
agacctctgc tttgccatgt ggcccattag gaatctgtgc tctcagacca tcctatgcat 108180
ctctccatct cagcactcat tactctttta tttttgtctc ttggcctagt tgcctcctcc 108240
tctttcacca cctcactatg aattaccttg agggtggtgt ccacacttct ttccagatgc 108300
ttaacttctc tttgacttgg ttcyctcatc tgtagaatag gaacgatact aatgcctact 108360
tgattgagtg gctgtgagga tggatgaatc catgtagaat acttggtcca gtttctgcca 108420
cctastaagt gctcatttaa tctaagctgt gattattaac actaytaaca atattgtgtt 108480
ttctaaatat atagttggct ttctatcaca tagagaactt tcttttcaca atttgctgaa 108540
taaatgaaga gaaaaagtag taggattttt tcttcctact gcaaaagaaa gaggtatggc 108600
tgtttattct gattcagatt ttctttagtg aaaaaaagaa aaaagagggt aaaagaaagc 108660
ataataactc cataaagagg aaagcgtttt ttttttgtt gttgttkttt ttaatcagtt 108720
ctgatttcct ttctggtatc tctgctggtg ttttcaaaac ttggcaactt tgtggctgtg 108780
gaagactgtt gatgagaggg ttgggcgatg atacctcagg gttaccctca ggtcgtacct 108840
ggtggtgtca gcttatcaga gccgwctccg ggtggtagta ggtgaactca ggtatctctt 108900
cttcagatat tctacagtga gaaatttttt tctggaaggt tggacatggg agtaaatcca 108960
ggccatacca ttcctggttc tgtttgtcag tatcatatct actctttgag atccaaagtt 109020
tgaggaatgg atagattcta ggtttgtctc atgttattgc tcagcagctt acagagtttt 109080
ttttttttt ttttaaagaa ttccacatgt gttcctgaaa tatgctctaa ctctgacaca 109140

aaatttcagt gtgcattagt aggaaaattg atgccttaca aaatatactt agcttaaaat 109200
atgtccatat tttaacttat aggaagagaa attctcgcag ctaacagggt ggaaaatgtt 109260
gaaagtttgg cttttgaytg gatttcaaag aatctctatt ggacagactc tcattacaag 109320
agtatcagtg tcatgaggct agctgataaa acgagacgca crgtagttca gtatttaaat 109380
aacccacggt cggtggtagt tcatcctttt gccgggtaag tgtgttcatg ttttcctaag 109440
agcttgaaac tgtatgtctt ttacagtcat tgaaaagtga tgccctaggg atttaggtaa 109500
gttcagcaaa tataagattg aactgtatwa gttgaaatca ccttaaattt tatttctttt 109560
ttcctccraa aaactttatt ctgggggagt aaaaaaaatt gtttttaaac ccaaaacatt 109620
tcttctaact tttggctttc tcagtcttca ctgaagagta gtttttttca cagttgcaga 109680
ggaccaaaca atgtgatata gattcagtag aaaaggagtg aataggcaac agaattaaca 109740
ggaaagaccc aaattctttc cctgctttaa tatatttata taaagcttag caaaacttgc 109800
ttaatcattc agtagttttc agaataaaaa gtttttcaga ccacaaagtt tcatgtttta 109860
ccattctata attggtggtg ccagacaagg aaagacagaa gagttcacag tattcctttt 109920
tggttcctac ttttcttatt taaatatgtt taacagctac tgtgtttatt tagaacaaat 109980
ctgagctatg tgttgtatat gagtggaatg ataaaaaaga tggctgctaa cccaccaatg 110040
cctgattacc cagggaacat ccatacctgt tcttccgtta gatatataat ctcatcagct 110100
tccaaagcta gtttgtgaag gaggtatgtg taaataccca ttttagagag aatgaatcta 110160
aggcgcagtg agataaagtg acttgtgaaa gggcccgcag ctattaggca acagtcagta 110220
ttcaaattcc agacctgtct gactggaatg cctgtgtgcc taaaaaagtc tgtttgctgc 110280
rtctagagta tctgctttaa tttcctctct gtaagataat aaaagaaaca cattttaaaa 110340
ctgatgttat tattgataag aaatttcatt gccctataga gagttaaaca gtttagtttt 110400
ttaatgaatt tgtcttaact caaacttttg gcctttggtt ttgaaaaact gttgaattcc 110460
tttcctgatg actcttttgt ttaaaatgat atgaagtagt tacatttcag aaagttacat 110520
tttggaaaag aataattttg attcctctgg atcccataaa agagaaaaag ttgtttttt 110580
attttctttt gttttttttg tgttttttkt ttttgttttt gttttttttt gcctctagac 110640
ttatcttttt cccactcttt agaatattaa aaaaatgctt gggtcagata ctgtttgcat 110700
tgcattgatt tggatgcttt cttcatctga gatgaatggt ttcctgcaaa tttatcaatt 110760
ccttatggaa gaatgactag aggatcctga atgtttaatc tagagagaaa gagattgaaa 110820
tgttttcttg ctctgttcgt tgtttattat tttattttaa taacgtggaa tatttaatag 110880
gtaacctgaa ttgtgtcttg ttagagaata tgttaggcga caatagtttt agttcctaaa 110940
ctctgagaca gtggttctct tctctcaatg cccatttaaa tgccatttgt atttgtgact 111000
ttggttacat gttaactaaa ttttaactga gaattacatg agttatacac taagtatgtt 111060
aagttcaata gcatataaag aaaacaaaat taattgcagt atctggagaa tctctgtttg 111120
ttctaaatct ctggaagtca tgtagtttgt cccagtgtta acagccttaa tttactactg 111180
ctttttctag gtatctattc ttcactgatt ggttccgtcc tgctaaaatt atgagagcat 111240
ggagtgacgg atctcacctc ttgcctgtaa taaacactac tcttggatgg cccaatggct 111300
tggccatcga ttgggcgtaa gtaggaatca tcatccccga tacttagttc tcttttactg 111360
cagaacacat aatgaggcag gttgggtgat atgatggtgt aaggaaactg gtactgcttg 111420
ccctcgcgga attttaaata attaattggt gatgggagaa ggatattgaa caagaacaca 111480
aaggacataa acatagttgg ccagctactg ctggggtgaa aactaataaa ttcatgagta 111540
ttctgagaaa attrctagag aaagctgaat gacaagattt agtggaaact caagatgggg 111600
gaggtgggtc ccaagcagca tttaaagtag ggtacagatt tgttgaactg taggcagtgt 111660
gtaatttctt acagggaaca tcttgagttt aggaaatctt tggagtcaat taatcaacaa 111720
atgcaccttt gcttacatgc actttgggag gactttaaaa gtataagcta tggttctcaa 111780
gaaattgatg atctatctag gaatatagga aaaggaatag agtaaataag cttataaaga 111840
tgaaatgcca argtaactta tgggagaaaa aaagggaaga aatatatttc acctttaaa 111900
catagattac taccamtgtt tttcttaact tgttgatttc acaaggagaa aataaaattt 111960
ctggctcaaa gatagcaaca ttttaagttt tctaagacaa ttgattgaaa gccacttcat 112020
gaaaagtagc cgtctctttc tgggggacat aaaactgtta aatttttaat gaatataatt 112080
taaattttaa aaactttgtt taataaatgt gtcaactgac cctactgttt ttggatgccc 112140
tttgtgtaaa gggtgctctg atagtttttg gataagagat aactaaatat tttattattt 112200
tagtgcttca cgattgtact gggtagatgc ctattttgat aaaattgagc acagcacctt 112260
tgatggttta gacagaagaa gactgggccr tatagagcag atgacacatc cgtttggact 112320
tgccatcttt ggaggtatgt tttaaagcaa taaaagtatg tattgttttt atacattgca 112380
agttacaata gtaaactcat cctcatgtgg cattttcaca atcccagaaa agctggccac 112440
tttaaaatga aaaaatttaa aatggtgcta tatatttaga caaaacattt ggtttgttga 112500
tggtgtattt cattttaga gtgtgatttt tgttttgtat atattcgtat aatgttgaca 112560
gtgtatatgg gtacagcact ttgtagatta catgtattat acaattcaac atcccaagta 112620
cttagttata caagtatcac gtgaggaaac agtaaattac tgccttcatt ttcaagaata 112680
aaacagcaag agctgtttat agtaatcatt gtagcatttc attattctcc agtgtttgta 112740
agaatctcat tagaaatcct tgtggaaaaa acgattacac atattcatca actatatgct 112800
gactgaatga ctttgaaact tttttattca aaatgttgga gaactgacat crtctttgtt 112860
ttatggaagt gttaggttat gctttatgaa gaacagcaag acataatttt ttttcgtcaa 112920
cctttccaaa taatttcatg ctactagtga agattgctga gaagcatgaa ttctggggaa 112980
ctacagtcac aatgagcaca gccartgctt gcctgtcttc tcagctcccc atttgagtgc 113040

aggcatgctg ctgtgagttg agtttctggg aataagaatg tagcctggta ccatgaaaca 113100
ggtggtttgc ttagtcttga aaacaggagc tctgtgaatg gttgtatagc ttgtgcactg 113160
cataaaaatg ccaggccaag agggtgagga gacactgaaa tctatcctgg gtctgtttga 113220
caaaccatga ttactccagt tagaggggtc atgttttgtt taagtctacc aaaagccctg 113280
tgtatatgct agttgtgtcc ctggttgaaa cctcctactt tgaataatta acacagtgct 113340
tgaaaagact agacactcac tataaatcaa agactttctc acatgcatag aatgtatgtg 113400
tggaatgaat agttagtaag tatattgcat atcttgtcct gctgtctgtt tatctgtgga 113460
ggagtgtgtg gtatttaaaa aatgctcatg agatttttga tgagttaatt ataaatactc 113520
ctcccgtccc cctcccgccg ctgccatcca tttactccct tttcactaat gatgtcagac 113580
acatgctatt tgctgtcaca tagaaacatt ataaaaagtt gaattttctc tgctctgggc 113640
tgggatgttt tgggattcga gaaaatgtag ttttagtatc ttttggtttc atcagtatga 113700
aaaaaatttg aatgcatacc catgaggaca acacaacatt cccaaaatag caataattat 113760
ttatttcttt caacattgct gttttttttt ttttttatta tactctaagt tttagggtac 113820
atgtgcacat tgtgcaggtt agttacatat gtatacatgt gccatgctgg tgcgctgcac 113880
ccactaatgt gtcatctagc attaggtata tctcccaatg ctatccctcc cccctccccc 113940
gaccccacca cagtccccag agtgtgatat tccccttcct gtgtccatgt gatctcattg 114000
ttcaattccc acctatgagt gagaatatgc rgtgtttggt tttttgttct tgcgatagtt 114060
tactgagaat gatggtttcc aatttcatcc atgtctctac aaaggatatg aactcatcat 114120
tttttatggc tgcatagtat tccatggtgt atatgtgcca crttttctta atccagtcta 114180
tcattgttgg acatttgggt tggttccaag tctttgctat tgtgaatagt gccacaataa 114240
acatacgtgt gcatgtgtct ttatagcagc atgatttata ctcatttggg tatataccca 114300
gtaatgggat ggctgggtca aatggnnnnn nnnnnnnnnn nnnnnggaaa tgcagaaatc 114360
accgtcttct gcgtcgctca cgctgggagc tgtagaccgg agctgttcct attcggccat 114420
cttggctcct cccctcaaca ttgctgtttt ttgtgaattt cttttggaaa gttcttttgt 114480
tgtgcaacac catagaaatt gtgtaccttt ttactaaagg gctagatctt cttgattgtg 114540
caccacacag aactaaaaga tttattgaac tccttactta tttaagtata tgaggatgcc 114600
tttgttagta gtgggactgg gattgccagg ctctagaaag atttagggag tccaatgact 114660
gattggtcat tgattagacc acagataagg aaattggtca aataaaattt atgacatctt 114720
aaacattttc tgattaatta gggttttcta gttaaactat cattaaagag aaaatccaca 114780
ttgatgcaat tctttctttt aaaaatatat gtttattttc ctgctgcaat agttagtgta 114840
aagtgaacat gattaaattt ttgttgttta gaatcttatg tcgcctctct cttaccattg 114900
tgagcatcat tctaacatta gtagtgtggt tgtaggtgaa tccacacttg tgttgagatt 114960
tttattgatc ctcaaacata cactgaaagt tccttttttg ggctagacct gtacttttcc 115020
ttctcaacag cttcttattt aagtcaaggg aaaaaaatta caatttaagc gctgtcatta 115080
aaacatagaa tatgaactgt ttgacctggg aaggatctca ggaatgattc agactgtctc 115140
cttcacacag cgtagtattt gcctaagagc actcagcagg tgagtgcttt agcgggtgca 115200
gacctatgag gcctcattta atgctctgta gaagaattcc ccaattctta ttttcactat 115260
tacctatgca gawctaaatc caattgctac taaatgccat cataaaactc catatgtgct 115320
tgcctgaacc tgaaccctga tattattaac atacagactt ccacagagca ttactaggga 115380
gtaacaagtc gtggaaaatg gttagagaaa catattacag atatttatgg gggagatgat 115440
cgtacttgca agaagcattt caarcctatt gcattttctc aagtgattta tttataagtt 115500
agctgtgact gaaaatacta atctacccat gtttcttttc agagcattta ttttttactg 115560
actggagact gggtgccatt attcgagtca ggaaagcaga tggtggagaa atgacagtta 115620
tccgaagtgg cattgcttac atactgcatt tgaaatcgta tgatgtcaac atccagactg 115680
gtgagtgaga ttgcccagtt ttttttattt ttttgtatgg gtttatttat ttgttacagt 115740
ggctcctgtt ctctttaagt acttattact taaaggtcta gctcctggta gttttatatt 115800
cttgtcgttc acataatcta agagtgtaag acttgaaatc tctgttcaat gctgctagcc 115860
ttaaacatgt tgtcaggaaa aacacatttt gggacttttc catacctaaa tggaatgttg 115920
tatttggcgg gttgatttcc aagaggaagc tacttttttag tattgggtct gaaaaatgtt 115980
ttgtcctgtt tgttttcctt cacaaatcaa acccgtgacc tacytagtga aaatgtacat 116040
gactgactcc ctcggggctt tgcttttgca ggttctaacg cctgtaatca acccacgcat 116100
cctaacggtg actgcagcca cttctgcttc ccggtgccaa atttccagcg agtgtgtggg 116160
tgcccttatg gaatgaggct ggcttccaat cacttgacat gcgaggggga cccaacmaat 116220
gaaccaccca crgagcagtg tggcttattt tccttcccct gtaaaaatgg cagatgtgtg 116280
cccaattact atctctgtga tggagtcgat gattgtcatg ataacagtga tgagcaacta 116340
tgtggcacac ttagtaagta gctatgcact ggcgatattt cctgggatga atagagtaga 116400
ggtgggcttt aaagaaaata aataaaagct tgggctattt atatgggaaa aatatctttt 116460
agaatttcag attcttaaca tgcactttga aggyttttag gaagctaagc aagaaatttc 116520
attcataatg ttatggatgg tttctggcct tgatttagac tatcttcaac aatwtttttc 116580
cttgacattg gctgtttgga ccaatgcagt cattatgtct tggcaaactc ctcaaaaagt 116640
caaatcgaaa taaactagat ctgaccaggc aaggtggctc atgcctgtaa tcggaggccg 116700
agacaggagg attgcttaag tccagaagtt tgagaccagc ctgggaaaca tgacgaaatc 116760
cggtctctac aaaaaatata aaatggcaca tgtatacata tgtaactaac ctgcacattg 116820
tgcacatgta ccctaaaact taaagtataa taataataaa taaataaaaa agaaatagat 116880
gagctcagaa aaaaatatgt atataaaatt acaaatagct gggactatta caaaatacaa 116940

aattacaaaa tacaaaaaaa acaaaattac aagtagctag gactacaggc acatgccacc 117000
acacccagct aatttgtatt ttgtattttc acaaaatttg taaaatacaa aaatttgtac 117060
ttgggaggct gaggtgggag agttgtttga gctggggagg ttgaggctgc agttagccaa 117120
gactgtgccg tgtacttcag cctgtgcaac agagtgaagc cctgcctcaa aaaaataagc 117180
aaacaaacaa caacaacaac aaaaaccaaa aataaagtag acctaacatt tagcaaccga 117240
gagaatagta tcacagaata actacttgca atcatagcct ttggaaaatc tcatgtgtta 117300
tattcctttt ctcccatgtt agagtaaaat aaattaacaa tgaaatggtg gtcttaacct 117360
ttatattctt cttttgacgg taatctagtc tatatagttt ggggcctaat aaacactatt 117420
gcagaaggca aaagtattac attcaaatta aaaaaaagat agaggacagt tgaaatctca 117480
gaaatctcta tcaaggtgaa gttaatacta ataataacct ttcttttgga gagaaagagg 117540
agtgacagat ttgcaagagt aaagtgctca cttgtacatt tttctgaaat tttttaaatt 117600
ttcatctttt tgtgtattat cttcttgttt ctaagagcac agcattttac cttaatattt 117660
tatctatttg cacttttcat atgacatatt ttcaagcttt ctatagtctg aatttgaaat 117720
tgtggttgga ggaagtaaca gcttgaaagt taaggatgag ctttagagtg aatccaacca 117780
gagcgtgaat cataggcagg ttcctaaatc tctcaaagac tcaatttcct tatctgtaaa 117840
atgcagacaa ttatatgtac tttatagtat tcttgtgagg atttaaagag aacttatatg 117900
atgtgtgtgg gtgcataact tagaaaaatg ccttttctat gataaatacc aaataaatgc 117960
cagccaataa tgatgttagt gatgatgaca tcacttgatg aacatttctc cttattatat 118020
acaatgcctc cattaaaaaa ggtgaactga gcctttataa ggcaagaact catttaaaag 118080
gctgtaaaaa caaatgtctt catgaccagt ttgttactat tgtagataat acctgttcat 118140
cttcggcgtt cacctgtggc catggggagt gcattcctgc acamtggcgc tgtgacaaac 118200
gcaacgactg tgtggatggc agtgatgagc acaactgccc cacccacgca cctgcttcct 118260
gccttgacac ccaatacacc tgtgataatc accagtgtat ctcaaagaac tgggtctgtg 118320
acacagacaa tgattgtggg gatggatctg atgaaaagaa ctgcagtaag ttttgagctg 118380
gtttcccttg gttggtcagc ctcstaaata gwcttcaaca accaaatggc cttgcattct 118440
ttcctctaag gctcatgcaa ttttcattgt ctctttagta cttctattcc acttgtcaat 118500
ctctgtgtca ataggttaca agaacaaagg cacgtgcctg cacatgggat tcttagagtc 118560
cacctacaaa tattgagttc tatggaagca aagcaaggac tgcctctgat gccaaacatt 118620
tcaattcaga taggaattga aaaagtgaaa atccctcagc tatctattta tatatttaaa 118680
acaatactaa aagtcatata gatatatcca gacctttggc tattgatgtt tmtttttcat 118740
ttggtacaag caaaaagaca tcaaaataaa gaggcacaga aaatttaaat ttcctttgat 118800
cttatccacc tgttttccat cttgccagtt ctgctttcct ttagcttgtt gttttatttc 118860
atgtcttcaa taatagttta agatggagca aagttccctg ggctaagttc tagtcctggt 118920
tgcctgacta ggcaagtcac tatcatttgg aatagatgag ctttaagatc ccttctagct 118980
ttcataccct ataagtgtgt atttaatata atttcatgtt gtgggtgggg ccagccactg 119040
catccgactc caaggctatg gtcttaacag taaggtagga ccctggtttt tagaattgtt 119100
ctgttcagac ttttaaatcc agttttgggg gtctgtctac acactgttgc tactaggcat 119160
gtgggtcatg ctggttttgt tgcctgattg ggctccattg cttggckttg gtctagagtc 119220
atggacttca tagtattcat gaaatgtagt ccaagtccaa gcacatgatg ctcactttct 119280
gaatgtggtc tattttccaa ggtgtaatca cagtttctga ctctgccctg taatcttttt 119340
attctcaatt ctaaaaccta tcctagtttt gagttctttt gcttagctga ctttgatagt 119400
gtggctgatt caaaagaatt ttgaacccat gtacaattga gataacttct gtagctattt 119460
agccattttt agtttggctc tggtacttgt tgcacaggaa ataaacttgt tggttttgtt 119520
ttcggatgac attagattcg acagagacat gccaacctag tcagtttaat tgccccaatc 119580
atcgatgtat tgacctatcg tttgtctgtg atggtgacaa ggattgtgtt gatggatctg 119640
atgaggttgg ttgtggtaag tgcattgcyt tckttttat tcacaatgtt tatttagaaa 119700
aatctcagtg ttaacacatg gacacaggga ggggaacatc acacaccggg gcctgttggg 119760
gggtggggag ctagagaagg gatggcatta ggagaaatac ctaatgtaga tgatgggttg 119820
atgggtgcag caaaccacca tggcacgtgt atacctatgt aacaaacctg catgttctgc 119880
atatgtactc cagaacttaa agtataacaa caaaaaakaa aaatctcagt gtttagtcat 119940
tttagccctg agctaatttc taatgctttt ctctttcatt cttagtatta aactgtactg 120000
cttctcaatt caagtgtgcc agtggggata aatgtattgg cgtcacaaat cgttgtgatg 120060
gtgtttttga ttgcagtgac aactcggatg aagcrggctg tcgtaagtaa cacataccca 120120
gmatgtttca gacaaagggg tcatttcatt tttgccagta ttgatattga tattgccaca 120180
cattttccct aactcagaca aactgggggа aagtatcctc aaaggaatgt ggtattgaac 120240
atacagtaaa attgagtaga cattgccata taatgtrtaa ttaacaaatc aagtggttgt 120300
ataaatggac acttcaaata gtctcttaga tgggctaaat atttcttaga tatttttgtt 120360
ttcactttta gtttttctta ggacttccca ctttagtagg tttaaacttt tgaggctcta 120420
ctccatataa agatatttta ctggtttctt ttaagtktca gtagagaagt catatcatgg 120480
tgtagaaatg gtatggagct gtgtttagta ttgactctga tgaattcatt ctttgtgcta 120540
ttatgtgttg aatatctgct aagatgttat ctatggagat tatagaaggc aagagacaat 120600
taagcaagat agacagttac aagggtctta gaaatggcac agataaaatt ctatggaggt 120660
tcagagaaaa gaaatttctt ctagttggag gattcaagta ggacttcata cagtataatt 120720
ctgatggatc tataatcttc acagactgga aacctatact cacatgattt gttatttgcc 120780
cacttttgt tttaaatgga ttttagactt gcaaaaactc atcagtgagt tgatcatttg 120840

tttgaacaat ggtgttttag accaaaaaag taagttttca tgaattctcc tcctgcgtca 120900
gaaaggtagt gtgtaaagcc atggattaaa aakaaaagtt aaataaaatg cttatatact 120960
ttatagtttg cacaacatct agaaattact aatcactaat tttcctgttt cacattaaaa 121020
acataaaatt ctgtgatgag ctgaggttaa actgtcaatt gccgctggct tgctgttgcc 121080
ttgtgagatc cctggtagag agttttggtt taccccttgtc aaatagggaa gcagttctta 121140
cgtatctctc caggattgct tgatgaatag tggaaagttt gcaaagaact gagtatttac 121200
catcatcttt agttagtgtg tgatggtttc attaggtata gttcatctga gggaaaataa 121260
taacacccaa acatgatatg aaacacatga agttcaaagt aatcatagct atttaagctc 121320
tattgtaatg ttctggtgat tctttcatag aaagatagat aaactttatt attgaatctg 121380
caattggaag tacattaaaa acacaggaaa aggaaacagg atgttctttt gacacaggta 121440
ctcatctgct agtcagcagt tgtgcgttct gtacttcgtt tgttgtcaga gccactagct 121500
gccacaaaga aatatttcta tgtactagag tgtgggagaa gactctatat catttagcct 121560
taaatattaa tttggtcata gttgttacta taaacctact attggatcca aaatcatttc 121620
ctctgagtct agactatraa agggatcaca aattacattc acaagccgat ttaccccatg 121680
ttttccttct agcaaccagg cctcctggta tgtgccactc agatgaattt cagtgccaag 121740
aagatggtat ctgcatcccg aacttctggg aatgtgatgg gcatccagac tgcctctatg 121800
gatctgatga gcacaatgcc tgtgtcccca agacttgccc ttcatcatat ttccactgtg 121860
mcaacggaaa ctgcatccac agggcatggc tctgtgatcg ggacaatgac tgcggggata 121920
tgagtgatga gaaggactgc cctactcagc cctttcgctg tcctagttgg caatggcagt 121980
gtcttggcca taacatctgt gtgaatctga gtgtagtgtg tgatggcatc tttgactgcc 122040
ccaatgggac agatgagtcc ccactttgca gtaagtttcc tgaccacagt ttactggcca 122100
taaactcatt ctgaacagta gcctggtgtg catcaccatt gtcacagtca ctgtgtagct 122160
ttgtaggaag gatttcagtt cctctatgag ttcacatctg tgtagggggt aaccataatt 122220
gaattcaaat acatcaccat tggataattt tctgattaaa tcctttgtac ttggttatgt 122280
gtttttactt ctttttatgt ctttgtttca aaaaatgaga ctaaattgag gccattagat 122340
tgtcaaatta aatttggttc tgttggtaat gtgctcatta atttttctaa ctttaatatt 122400
ttctaatttc aatcagaact tatcacaaaa aaatgaagtc cagggatttg tgttgctgtg 122460
attaaagtgc tgtgattggc atgtaatcct aattactgtc atttctttct ttcctcttta 122520
atcaatgctc actctcagat gaaccccagc caggtatgat tgtgaagtat ttcagattct 122580
tatgatttca tatgtgttgt gtttgttctg aaaatgtcct gattatatta acttacttcc 122640
ctttctaacg catgttctgt gttatgactc ttacaaatat gttagagtac acatggaaat 122700
agaaggcatt tgcatcycca ggcatgtgaa ctgtcttagg gtggctttag gcattttcat 122760
tttggccctg aaagtaaggc atgacgatat gttaccggat ctgtgtactc taatatttca 122820
atgacctttc ccctttgatt tgttcacttc atagattttc tggtcttttc tcttaaatgt 122880
ttgtctatct tccatttctg tatagatagt agaatttcag aggaagaaaa cgagaaacaa 122940
ttttaagtgt ctttgcatgc tctatcaatg acacttttct tccttgatgt caacaatatt 123000
ttcccaaggg ttctcattgc attaaatgga gttatactat tgggttgtag tgaagaaggt 123060
gatcatactc caatggatat gaaggatggt aaatcctcag acaaattaga gcaaaccctg 123120
aacagcctgt ggaactcacc caagtgcatg ctgcacttag ctcttgtctg ggcatcatat 123180
tgaaggtggc atgagactgc ataataaata ttgcataaga gtgaatcaaa gaagcaaaga 123240
ttcttgattt tctttttca ttattctctt tcttttytct agatgggaac agctgctcag 123300
atttcaatgg tggttgtact cacgagtgtg ttcaagagcc ctttggggct aaatgcctat 123360
gtccattggg attcttactt gccaatgatt ctaagacctg tgaagacata gatgaatgtg 123420
atattctagg ctcttgtagc cagcactgtt acaatatgag aggttctttc cgstgctcgt 123480
gtgatacagg ctacatgtta gaaagtgatg ggaggacttg caaagttaca ggtaattgct 123540
gaactaaccy gagccagttt atcagcacat cccagagctt aaaatcaaat ggcacatgta 123600
ggtatttgac aatgttgatt aggagttaga tcgacttgaa tcctggaaag attatgcaat 123660
ctctttaaac ctcaattttt tgtgaggatt aaatggggta atacacatta aaatcctggt 123720
gtattttgga aaatagaggt taaaacatat acaagtcaat gatttttaaa gtatttaaaa 123780
taataccaaa tggcttttat ataatttaaa atgagttcta tactatattt aagcatcttt 123840
atataatgct taattgaatt caaccagtat taattcaatt tctgctataa gaaagtgctt 123900
tttactatgt attaggatat tgatttgacc actttcaaag tgaccaaata gaggaagcta 123960
aaacaaaaac agaaagtttc tttcttttac atgtagtagg agtctggatg tcagagagtc 124020
cagggcatgg ggtctgctct gttatcctca tcatgtggct tacatcaagg gttccaatgc 124080
tccaggtttt agcttctctt agaaagtagg aaggggaaag agaaagtgga gggcaagcag 124140
cttccttttt agaatgtgac ctgagatttg attcgtaatt tctactcaca tcctattggt 124200
cagaacttag tcatgtggtc actccaaact tcagtggagg gagagaaatg tctctggctg 124260
gagagtctgt gccaagctaa aacttggcat gctttattac taaaaagaaa aagaagagag 124320
ggggtgttgg gagaattaga actctctacc atagctgagg gcctcagaaa acagaaatat 124380
ttaagacatg attcctgctg tccagaagcc tacaacctat taaatagtaa ggaagataac 124440
caaagtacaa aaatraatac agtaaaagga agaatgtaag catagtttac tctagactag 124500
tatttagaaa cacagttaaa tataacccaa gaaagagtct attttaagta ctcatgaaaa 124560
ccagctaact attaaggtta agaatgaagt gattaaaatc attcatatgg ggcttcctcc 124620
cctccccacc aacttactat agtttggaat tacaccttct ttctgttacc aaaagtattg 124680
aatcaaaagt tttaaagagt tgttttgtgt tttctcccag tatcattgac atttttgcat 124740

```
tttttttcttg aacagcatct gagagtctgc tgttacttgt ggcaagtcag aacaaaatta 124800
ttgcsgacag tgtcacctcc caggtccaca atatctattc attggtcgag aatggttctt 124860
acattgtagc tgttgatttt gattcaatta gtggtcgtat cttttggtct gatgcaactc 124920
agggtaaaac ctggagtgcg tttcaaaatg gaacggacag aagagtggta agtacatttc 124980
tgttgacctt tggcctggct agttcctctg tcttgggtct gtttgctgtt attcaccagt 125040
gagagaaggc cctacctcat ctgggtagct ctcatggtac cttctgggcc acatcatacc 125100
caagagactt gcgtgttcat aactacgaat ttatggctgt tttagatagg agggtggcct 125160
ctgaatgcag atgtgtgatt ctgaattcca ggtcaggtga tgcagagacc tcacaatgtc 125220
tttacggttc cttttgcagt cttttcttgt ggatgagagc agaggaaagt gcaggaaagt 125280
taaggggttg cttttcttag ctttaattta gtgatatttc tcaatccatc tcccagaatt 125340
tcagtttctt ggctcctgat agttacattt cctctgcctc ttacaacttt attttgtart 125400
tcttggtcct taattaatag agatattatt cgttgcatgc aaacactata acattttgta 125460
atgttgccaa ctaagcaaat ggatagagct ttttcttaat tgcaaaaact tttgaaacca 125520
aaacgaaact atgcactaac caaacaatga agtcatctta gaatgttcag tgtgacaaaa 125580
tcttgtatac ttttctcaga aaaccctgct gttgatttgg tggttagcta catgaggaga 125640
caaaattttc taatccccac aagtaattat aggacaagtt agatggttta atctagattt 125700
ttatataata tccatgtttg cattcattta tttgctctag aattcactct ttattcactt 125760
ttgtctttag gtatttgaca gtagcatcat cttgactgaa actattgcaa tagattgggt 125820
aggtcgtaat ctttactgga cagactatgc tctggaaaca attgaagtct ccaaaattga 125880
tgggagccac aggactgtgc tgattagtaa aaacctaaca aatccaagag gactagcatt 125940
agatcccaga atgaagtaag actttttttt aaaattatgt tgccttgaca tggttatgat 126000
gagggaaaaa caacagtaac atgatgtagc tgatatgcat gttgctgata ygcaaaattt 126060
aaaatgatcc cttgtttaaa catggtaggt gtccaactgg gtgttgctat ctctccttca 126120
tctgaatcat cctcttcata aagtacataa gagcaattga ttgtttactt tattttaaga 126180
gcacattgat ttattagctt ggcaatacaa tttttgaaat gtcatataat taaaaattaa 126240
gtttctaatt actgcatgca gtaatagtcc ayagaggggc cagtttgatg taactttgat 126300
aactcatgat tatacaacaa aaaagctgga tttttctgct tcagttttat gttgtttatt 126360
agagctccct tttaagtcat ataaggaagg cagtttttgc ctgctgatcc tgaagggaag 126420
atagagaaat tctcccatgt gtttggaaat ctttgaggat ttctttccct gaatttactt 126480
atattttata acttagattc ttttctgcag gatggtaaat taggcaagtt atgttcaatg 126540
tgatgttgaa ttcctagata ttgtaaagta ttacacacca ctgaaattta tgatgaattc 126600
ctgatgaaga ataaattgat ttccttatct aaaaacatga cagggtagac aaacaaggac 126660
agatggattt ttctagatca actatttgtg gattataaac aaacatgaat tggcattgag 126720
acatttcaat gtcataatgt actacattat gacattatgt attacatgtt ttatgaacat 126780
tataaaaata cccagatggg ttgtgattgt gttatgacag ttttactttg tgacacttag 126840
aggaaacaat aaactctgtg aatatattct gaaccagaga tgatttattt taagcagggc 126900
ataaacagga tgwtgtatta tttaaaatga cagttatttt taatatttaa atacgtcccc 126960
tccaaytggt aactcatttc ctttcccagt gagcatctac tgttctggtc tgactggggc 127020
caccaccctc gcatcgagcg agccagcatg gacggcagca tgcgcactgt cattgtccag 127080
gacaagatct tctggccctg cggcttaact attgactacc ccaacagact gctctacttc 127140
atggactcct atcttgatta catggacttt tgygattata atggacacca tcggagacag 127200
gtgatagcca gtgatttggt aagttggtgg tgaggaaaac caaattaaaa ctacagtcgt 127260
ggataggtag aaatcagacg agtatcagaa aagctaagaa attaattttt gtgtcataga 127320
cattgtcaga tcaatccagg aaataccagc aacagtgaga ggcagtctat cccatatgac 127380
taactggaaa atgaatattt tcattccagt tcatggtcag cttgtgccat atccaggaag 127440
gatttttata gctcgtgtga tttagttgag ctgcagatgt gaatctgttg cttctatacc 127500
tttaaaaatt gtgtcaggtg gccgggcgcg gtggctcacg cctgtgatcc cagcactttg 127560
ggaggccgag gtgggtggat catctgaggt caggagtttg agaccagcct ggccaacatg 127620
gtgaaacctc atctctacta aaaacacaaa aattagccag tgtggtagca cacacctata 127680
gtctcagcta ttcgggaagc tgagacagga aaattgcttg aacccgggaa gcagaggttg 127740
cagtgagctg agattgcctc actgcactcc agcctaggtg acagagtgag actccatctc 127800
aaaaaaaaaa aaawtttttt tcaagcaaaa atttataact taacttggcc aggcacattg 127860
tctcacatct gtaatcctag cactttggga ggctgaggtt ggtggatcgc ttgagcccag 127920
gagttcaaga ccagcctggg taacatggca aaaccccatt tctacaaaaa aatacaaaaa 127980
ttagctgggc atgggggtgt ttgcctatag tcccaactac ttgggaggct gaggtgggag 128040
gattgcctga acccagggag gtcaaggctg tagtgagctg tgattgtgcc actgcactcc 128100
agcctgggtg acaaagtgag accctgtttt caaaaaaaaa aaaaacaaaa attaactaga 128160
tttatatttc tcagtcttgt tcttcacata acatttttta ttctataaat tctgttgaat 128220
ttattttcac aagttaaatg ggaaaataaa gaaaatagat attttatcaa agagctgtta 128280
ttgaccccca ttaaaaatag gaatgctttt acactgttgg tgggagtgta aattagttca 128340
accattgtgg aagatagtgt ggcaattcct cagggatcta gaaccagaaa taccatttga 128400
cccagcaatc ccattactgg gtatataccc aaaggaatat aaatcattct actataaaga 128460
cacatgcact catatgttat tgcagcacta tttacaatag caaagacttg gaactaacam 128520
aaatgcccat taatgataga catatacatc atggactact atgcagccat aaaaaagaat 128580
gagttcatgt cctttgcagg gatatggatg aagctggaaa ccatcatttt cagcaaacta 128640
```

acacaagaac agaaaaccaa acactkcatg ttgtcactca taagtgagag ttgaacaatg 128700
agaacacatg gacacaggga ggggaacatc acacaccggg gcctgtcagt gggtgggggc 128760
aaggggaggg agagcattag gacaaatatc taatgcatgt gagggttaaa acctagatga 128820
tgggttgatg ggtgcagcaa accaccatgg cacatgtata cctatgtaac aaacctgcac 128880
gttctgcaca tgtatcccag aacttaaagt aaaataaaaa ataaaaaatt aaaaacaatt 128940
taaaaaagag aaaaaattgc tattgtatag ttgctgtgac ttgaaggaaa gatgcatcta 129000
aactataaca gattgatgtg aatcagtgag tggcagcaca agaccgtgga aatagccggc 129060
acaagtgtgc tgatggtgga gtgaaggctg gggcgtggga gtgggagatg aggagtctct 129120
aagctctcta gttccatcta acttttaact agtaggtgat ccggatacat caccttgctt 129180
tttgtgcttc agttttgttt tcatttgtaa aatagatgcc cagtgtaatt accaagrcaa 129240
acataaagag taaatggcac gtgtatgtga aaggctcttg aatggtttag tgggatatag 129300
gacgaattgt gtatttttg ccgctctttt gcacaatgac ttccttgtgt ttttattaaa 129360
taatgacatg ttaaaggaaa ccgtcttctt gagcagatat cctctttgac tcagtgcacc 129420
ttggctttsa tttttggatg aggtctcact gttctcttct gcctcacaga ttatacggca 129480
cccctatgcc ctaactctct ttgaagactc tgtgtactgg actgaccgtg ctactcgtcg 129540
ggttatgcga gccaacaagt ggcatggagg gaaccagtca gttgtaatgt ataatattca 129600
atggcccctt gggattgttg cggttcatcc ttcgaaacaa ccaaattgtg agtgatacag 129660
agaaacatcc tgcctgggag tagcttgaaa aacactgacc ctgggaatgc taaatgyaca 129720
ctgttacaga cccatttgtt tggrcaatac attttccttt tctctttaca aaccacccca 129780
ctatatactt tcccctagtcc tgacattgcc attactttta tttaccatgg aaatttcaaa 129840
cctaggatat aataacagca catctgaatt atatcatttc agcatttggc tgctacctct 129900
ktgaccctca catgagtctc cgtttcctca gctgacaaat ggagtacaga ccagatagtg 129960
ccttcgatcc tcttaccgct accactctga ttgaaagcag cttactttta ggactagttt 130020
attatggcac cactgccttc taggtgctct gctgtagcca gcacgagttg tcctaaagtg 130080
catggtaygg gtgtctaggt gaaagacttg gcatccgtac tgttctttct ggtgggagag 130140
ggagataagt cacttartct tcacttaatc ctctctcctc aaaactctcc aattgtttct 130200
cacacccttc agcatgtggc tgctgctatt tccctgctct cttctcccac tcgctgttgc 130260
cacattggat ttcattatgg tccaaaagca cagcaggcga ctcctgcctc tcagcttctg 130320
cgctagctct tccctctrcc tggaacatct ctcttccaga tctctgcatg agttgcttcg 130380
cgtgcyattt aggattctac ccaaatgtca ctttctcaga gaggccctca ttgaccgctc 130440
tacctaaaat agccacccccc tcataattct tttgcyctct accctcatgt tctgaaacct 130500
ctctctctct ctctgagttt agttgtttct ttttgctcga atatatactc cacttttata 130560
gcgtccccar tgcttagaat ggtgtttggt ttacagtgaa tacctaccat ttttctggtg 130620
aatgaatgga ttaataatct attaataaca tggtatgtgt aataaaaatg tataggatct 130680
aggaaacatc ctgtgtgtgg ggaccacaca gaatcctgat tttcaaggtg cagagacaca 130740
cagagatatc atcagtagaa aaataaaaga ttattatcta accaaaatct ggaaaactct 130800
aggtaaacta caaggtcaca catcaaacac acaacttttt ttttttttaa tgcaaaaaga 130860
tctcttttag gtcaggtaag gagacagatt atttggcatc atatttctat tacaagttcc 130920
agattactca gtggctgttt gttcrtaatc cagttataga ctggattgat ctgtaacctt 130980
gagtcattct cctctctcgt gtctcttatg aattctaagt tgaaagcctg atgctaggga 131040
agttgaaagt gtgagtagtt crgtgaaaac aaaacaaaag aaaacaacag rggtaacaac 131100
gtacttaagc mcccctgtac tggggcctct ggaaggacac taagagcatg actctgtttt 131160
gattttaatg tggaggtttt ccacttactg gtgctttctt ctctttctca tgcagcygtg 131220
aatccatgtg ccttttcccg ctgcagccat ctctgcctgc tttcctcaca ggggcctcat 131280
ttttactcct gtgtttgtcc ttcaggatgg agtctgtctc ctgatctcct gaattgcttg 131340
agaggtatag tatgctcctt atgtgagctc tgaagatgga gctggtcata gtttgtgcca 131400
agcagtggaa actctaaaac caattgcgac tgaacatgtg ctgtgtcctt tgattcctca 131460
ggtgtctgca gaatgatgtg tgttgtatgg ggtgatgtca ctgtgtgcct tggttgtaat 131520
ayagtttctg tatatggaac taatgttatc tgtgcatgta attgaacaat ctgtaacctc 131580
atattttctc tcacctgggt acagttagac ttctctgaca agccatgata atgggaagtt 131640
ccaaattctt cacctaagaa gtaaacattc tcaacgtttg tgtacagctt catttttat 131700
gtccattgtc tctttctccc tctttttttt ttctttttc tttctttctt ttttttttct 131760
ttctgagaca gggtcttgct ctgatgccca gactgtagtg caatggcgta atcatagctc 131820
actgtagcct ccactttccg ggcccctgtg attctcccac ctcagcctcc tgagtagatg 131880
agactatagg tgcacgccac cacacccggc taatttttgt attttttgta gagaccgggt 131940
tttgccatgt tgcccaggct ggtctccaag ttctgccctc aggccatcca cttgccttag 132000
cctcccaaag tgctgggatt acagacgtgg accactgcac ctggctccat tgtctcattt 132060
ttattcttat aaccaatagt taatgagtgt tctagcctgg gtcttctgac tccaatttca 132120
gtactgttac tattaccatc tgatacttta agaaggagaa ttgtgttggt atgagatatt 132180
acaagtgact gagcaattta atatttatct catcctagag atattttatt gggtcgattg 132240
aagagtgtgt ggaggattat accaagtact taagggagta agaaaagaag gaaaagttgc 132300
atccagttca caaaagagat ttcttctgga gtgtgtactt gtatataata cacttaaaaa 132360
tataattcct tattgcttaa aaatctaaga agttactcta aacccaagtt ccctttcgtt 132420
tctcagtgaa gagaactgaa tgaatatatt ttgatactga tgaaaattgc tgtagacaag 132480
ttcaacttaa atgtttaatg atcacatatt cctaaattaa gagataatag agtcctaatc 132540

tagaaggaaa tttagtccta atctagaatg gaaaatatat actgaattca ggaaactttt 132600
agtgtttaga tattatgcag atgtaggctt actgaaaatc aaattccatc agcatgtaat 132660
attgtgcaat gatactttca tgatgaaaga ttttaattat tggtaattct cacagaggga 132720
ctggcacttg ccatttttcc tcagagactt attatgtacc taatcctcgt tgacattgtt 132780
taatttagtg tgttcctaga gtctttcagg agaagattaa actgggctgt agacatttcg 132840
gatacaaagc attctttcag cacacaaaga ctgttgaatt gcacattggg ggttggtgta 132900
atcaatatta ctctctgatg atgattgata agtgttaatt ttaaatagtg ccttttgttg 132960
tttcacaaat aattccacta gtggttttct catgggttga ctttaccgaa gtggaacttt 133020
ttaagtattt cccagtaggt ttcagagcac cagctgagta actgattgcc aatatatgtt 133080
aaatgaaaaa aggtttccac attttttttt ccccaacaag aagtttagaa aacttgttaa 133140
catttatagg tggaaacatt ttacttgatt tgattgttga atagcttttc aactagtgtt 133200
tactaagagg ctggaatata tgtagaagtg cttctgtgat gctgttaagt aaaagaagca 133260
gatattgcac aatattggcc ttgtaaaaac atgcattaaa aaacacacaa gtttctggaa 133320
gcaaaaacac acaagtgcca atagtggtta cagttggata ggggaattat gagatggttc 133380
tacttatttc taattttatg ttataatgag tgctttctct gtatgagact ttttaaattc 133440
tttagaaaat atattcccca caatgccaaa accaaatgaa caaacaaaac tcaagccaaa 133500
catcacctca gcacccctaa aattactcca aatacaaata gacttctgac tcggtctcag 133560
gggcacaagg cacttgcttc agtgattttg tgcaagataa gagaacactc cttgtccttg 133620
ctccagggaa ggctgcagtg ctgatcagct tgtgcagggt atgacttaag gaggacctag 133680
gtttgggggt catatatatt gtcgttcaat tacaacactg agttctcatt cctgactata 133740
gtgtcttcat gactctgctg acactaacat taatgggatt atgacatgga aaatagaaat 133800
gaagagatga tctttaactt caaaagacag agacacactg acctacttaa ccgtcaccac 133860
ctcctgaatt cctttccatc caaccctaga tgattctgtg cctacccctt catgccattg 133920
tcataattgt aagggctcat atacttggtc ttgccctcta gatgctgcgt tccttgagga 133980
taaagcctct acctggtctg tagatgtatg cttattgcct gtggcacttc rtggtacatg 134040
gtggcactca gtaaatgttg agtgaatgac aagctctcca atatccattt ttgttacttc 134100
cccagtcctc tgatttttac ccgtttgctc cgtagaaatg tgtgcagtgt tgtgaagtca 134160
cttctttttg ctttcccata tagcactttt caggcatctc cctgcgccac ctgttgtctt 134220
actggccagt tcctttctat tactcccctg gcatcatccc ccaccatgat gctcacagtt 134280
tcagccagcg cagcattgca ggagatcctg ttctctggtc cattgcttgc aaatgttcat 134340
tggtggtaaa cgttctcagt acatcagcag ttatcagata aagggcttga gacatgatcc 134400
ccaggaagca gtagaagcgg gtggtgctta agggaagagc accatggaag agtcaagaag 134460
gcccatgcat aatggatgag atatgcaaag tttttaggcc ctaaacaatg ctttggttga 134520
gaattattcc aattaagcaa agggagatga cccattcaaa agggcaggat cagatcttac 134580
gtaagtgagt aaaaatttaa agtyccccat aaaactggga cagagatagt ttctactgag 134640
ccagtgaaca ttaataacag ataatcaata aataattaaa tatcatctca atataatttc 134700
ttggtacagc tgaaactcat aatctagcat ttttttttt ttttttactg ttgcagttaa 134760
accaaatgaa atgagtggta atttgatact caagaaatag tacctggcct gcggtatttg 134820
cagtgtagtg atgaaaaacg tagattttgg agtccaggag tcctggttgt gtgacctcgt 134880
ttaaattgct tgatttcttt gtgtcttatt tgcaaattga gggaggacct atctaacaaa 134940
caagattagg aaacttgagg gagataaatt aagggaaata cttacctgat gcatgcagta 135000
tggcgcatat tctcaatcaa tgagaagyga tttttattgc aattgcagtt gttcagaaga 135060
gaggcaatgt ggagcagctg agagaagaag ggcctggaag tgaatgagcc agggtccatc 135120
tcctattact gtttcctgca gaagtcacag agctcctgca aatctcattt gctccagctg 135180
aaaacaactt tgcaggcttg ttgtggaaga ctctacattg tagtacttga aaaatgtaaa 135240
gcattaatag ttgcgaaatt tacattagac taaatttaaa tttgtcctag gttaataaag 135300
actgggttat ttctcagtaa tagaaatgat aggaacaaga aaaagctaat gagatgtgaa 135360
aataagtaaa gaaaaaatga ccaagtcatc ctgctgaaga tggaaagctt cccggattat 135420
aaaaataatg aaaacatcat ttttagctta tgaaagttgt gtaatgatta atcatttcat 135480
actttgtctt aatatgtgat atatcttata catatatctt aacccaaaac ttagattcaa 135540
aagttttcct tttctcagag aggaatttta aaaccccact cttgatgggg atcaggataa 135600
agattaaatt atttttgaaa aaggaacttt tattatctat taaggagata agtgaactga 135660
tagtttaaga tattatggga atgtttaaat tacaatgtgt agacagtttt gagaactttg 135720
gaagatactg tttacttatt cacttataca ttcatccatt aatgcagtca tatggtcatc 135780
catttagtta kcaaacattt attgggcaac tattttatgc caggctctga gtaccaggcc 135840
ctgggacaca ataatgagca aatcagacac agtcattgac ctttgggagt taaaatctta 135900
tagggaagag agacactagt caagtaacaa ctgataggat tatacattgg atttatttat 135960
taaagtctca ataaatacta ggcaacactt tgtagtgttg ttttatttt ggaacattct 136020
taaaactagt aagctgcctt tcacaagaat agtctcaatg attttttca ctttttttt 136080
ttcaaaactc aactctcctt tccctgagat cagtgtgagt gaggtttgtc tgtgtgtaga 136140
agtggaagaa cttcctgtct gtgaggttta gcaaacatgg gtggtttatt agtgtaagta 136200
aggacttaat gaagagtaag ataaatacca acctgccttg aaaaagtcca gacagcgttg 136260
tatgtggggt tggaggtctt gtggtccagc agcccactga aaccctggga aaggcccatg 136320
cttgtctgat gaagtacatt atatttattg ctgcaatgct gcaatgtcat tttagcccat 136380
atgatggtaa caggctattg ccttccatta ctctaaatgt ctgggaatag trggatatga 136440

ttttgactga tattcttcta ttttcacaga tgatcaacct ttcttaataa ctgtaaggca 136500
acatataatt tttggaatct cccttaatcc tgaggtgaag agcaatgatg ctatggtccc 136560
catagcaggg atacagaatg gtttagatgt tgaatttgat gatgctgagc aatacatcta 136620
ttgggttgaa aatccagtaa gttttgaata acattcaaag tatataattt attcttgaag 136680
agmctgcctg cactgatgtt ttcttataag caaacttttg tcatgtgagt aaaagggaaa 136740
caatgtggaa ataaatttat ccctaagttt tttgattcaa tgaggggtat awatktgagc 136800
ttggcctgga gcaaaaatca taacactctt tagcttcaga ataagaaaca aatttaagct 136860
attgtgtatt atttactcat tcagcaagta ttttccagaa gtgcctatga tttgccctgc 136920
actgaattac ctgcttctaa ccacagaata catgccaaga agcagcagtc acaatgcttg 136980
cccctagagg agtcttaagc tagtagaaaa tattcgacga atataaaaat gatcaaaact 137040
caagayaaaa gtagtagctc cctaagggaa tttagtgaaa gcatttgatg tggtgctggg 137100
gccttccttt agaatccttt agaatatttg cctctagggt aagaatgaac acttctccag 137160
ttctcttcct cagaggtcat tttcttcagc cttcagggaa aaaacctgta agaataggga 137220
aagagcaaga agactataaa ggaggaagag aagaaaaatc tttgtgtttc atgtttgtca 137280
cctatataca aaatatactc ctggtcttct gatccacatc tgtgacttgg gtttttctca 137340
tgacttgtat gcttgtggta gttaagaact atctctgtag ccagtactgg agatagcctg 137400
aatggtaagc cttgtgtatt cctgtgacac actgaaaaat cgtttgaagc ctacccagtg 137460
gtgctgaacc tttgtttgcc tttcctctga gtgtaaggac tgttcaagaa atacagcagc 137520
tggcagtagc cacagtgaag aaagggttct tttgyaggag ccatggcctt ggaactgctc 137580
acctcccctt gtctttcttt ccagggtgaa attcacagag tgaagacaga tggcaccaac 137640
aggacagtat ttgcttctat atctatggtg gggccttcta tgaacctggc cttagattgg 137700
atttcaagaa acctttattc taccaatcct agaactcagt caatcgaggt aatgattcca 137760
taatactact tacacaaaca ttggatttag attgatgtaa actctagtct caggaataga 137820
tctcacgtgg attttggaat catttttaag caaaaagaaa aagggaaaag atattagtgt 137880
taactatcaa agtctctgaa gtgaaagagg aaaaccacct taaaattttt tttaaattta 137940
tttttattta tttatttatt twttttttag acaaagtctc actctgtcgc ccaggctgga 138000
gtgcagtggc aagaccttgg ctcactgcaa cctctggctc ctgggttcaa gcaattctcc 138060
tgtctcagcc acccgagtag ctgggattac aggcgtgcac caccaagcct agttaatttt 138120
ttgtattttt agtagagacg gggtttcacc atgttggcca ggctggtctt gaacacctga 138180
cctcaagtga tccacccgcc ttgacctccc aaagtgttgg gattataggc atgagccacc 138240
acgcctggct ggcaaaaata aattatttga gctttctatt gctctatttt gtttcctcct 138300
aattatcaat actaccttgt tgctataaaa gtrttttagg taatttacaa aataatatat 138360
aagaagataa ataaaagttg cataaggaat tcaacataaa gggaagatta tggtaagcag 138420
agaattttac tatgtttcct catctaatct tcaatgctat ttcagttctc aaccaaattt 138480
atagtttgcc tctgttctta gatggaaatc tttctatggc tccagtacag tttttctaac 138540
agcaaaacag aaagtagaaa cttgattcta attcctttga tactctcttc ttcaagataa 138600
gtgttctttt tactctaatt cccagaagaa attctagatg aggcacaggt atgaaatcac 138660
atgaagtaag tcagaggtaa cttgactagt gttggtttgc tccactctga gagaagggta 138720
aaacatggaa gggattatta attcacaata attttgaaag tgaaacttcc caaaacaagg 138780
agaagttttt ggaggggggat agttagcaga gccctgacaa tccactgctt taggtgggca 138840
ccagctggca agacggtttt tctctggagc attcagaaag atactgaaga tgagcaaggc 138900
gcacagcagc ctgctggcta atttagagca cctatctata ctaaaaagca ctctctgtag 138960
actaagaaca cagcctatgt agagttcggt actatctgag gtttcatgca tcccttggtg 139020
atcttggaat gtatccccca tggwtgagtg cagatgactg tttttatttc tgccaaatga 139080
agaaataggg aaaaggtgtc ccaggcagag aaaagagctc tcactggaac agcgcttgag 139140
tttacaaaga tctttcacta gcatctaatt taatcctcac aacattcctg agggcaggca 139200
gktctggtag ccatttgtga tgagagggaa atttgcagtg tgcacaagta tctcaagcca 139260
ggtagaatta tcaggtgtta acatgaaggg ccccttggag gctcctctgg ttcaaactct 139320
ttttttttatt tttatttttt tacatcagaa accaaggccc acaraagcta agaagatgtc 139380
ttaaatggtc agcttcactg ctctaattcc tgagcagtat tctctctttg cacttttata 139440
aactacaact ccggcaatcc agactggttt aaccctcttt gacagtggca gaaaatattt 139500
ttcatgattt caactaagac tatcatcctc ccattaaaca ggcaacatct actgcctaag 139560
acccttacta ccaaactcac atctctctaa agtccaccca gtgcaaagct gtcttaattc 139620
caaatggcaa ttaatatgct cttattttat ctcttkgtct cttgattagt aaatggggtt 139680
ctcttctttt aaactgatag ttttccaaaa gcagggaacg tgtctttccc attagtgtta 139740
ggtacaatgc agtagtggcc agttggagaa taactgagcg tgcatgtgtg tatggattgg 139800
taaggccact ttaaccacat gaaccaaaag tttctaatta tgccctgatg cagtgtggta 139860
cagaggaaag atattttgat ttggagtcca aagacctggc tttgagtctg ggttgcttgc 139920
tcattttatt cattcattta atgagcacta ggaaatgctt tctatggatc agttgatcct 139980
ggatatccta agatgaataa acatttttt tctgtcttta agtagctcac atatctgtga 140040
gatggataca taaacaaata cctgtgctcc agtgtcataa gtgtgataag gccggtgaat 140100
ataaagtgct agtgattgga ggcagaggta taagtgaggg gagagagcat gcagatttcc 140160
cattcatggt tacttgtgag ctgagtcttg aaagatgact aatacatcct tgcttatcgg 140220
agggtttcac tttccgaggt ttcagttacc tgcagtggcc tgagaatatg tgagtacagc 140280
acaataagat atttaaaagg gaggagagag agagagacca cattcacata attgttatta 140340

cagtatattt ttataattgt tctattttca gattatggtt aatctcttac catgtctaat 140400
ttataaatta aactttgtca taggtgtgta tatgtaggaa aaaatatagt atatatagca 140460
ttcagtacta tctgaggttt caggcatcca ttggtgatct tggaatttgt cccccatgga 140520
tgaggggggat gactgttttt atttctgcca aatgaagacg tagggaaaag gtgtcccagg 140580
agagaaaaac agttgaataa agaccctgaa acatggaaat gcattttatg actggggaca 140640
acactgcatt ttctccactc atgagctatt cgaccttgga caaattactt aacttctctg 140700
agcctgtttt ctcatctgta cagtggagtt tatggctgag gaagtaaaag tacttcataa 140760
cactraggta tcctgtaaat acagagygct gtttccctca aatgatcaat atttttagaa 140820
aatccatgaa agacctgtga gaataatgat ccaagggcaa actgcccttt taatggttta 140880
actggtgttt ccccttaggt catttaaatt gtaagtaagt cttccaggtg attgttggat 140940
taattaagaa aataggaatc rtattcactt tctgtttacc tgtataatat tccttcctgc 141000
ctaagagtag ttcgtgttta actccaactt gaaaataaga gaaacattga agaaactatt 141060
atccactagg ggtagctgtg ttcccatcca ctaaaagaaa ttttatagct gaattttgta 141120
gtgaagccta cagaatggcc gtgtgagaga gagctctata tattccagaa agcaagaaaa 141180
ggaactgtga accaaagaga tccttagtct taggaaaagg agagagattg tagcagaaag 141240
aggcaaaccg agaaaagaaa agctacctta gtccaagcaa gagtgaaaga taccagacaa 141300
taggcagaga aaaaaattta gagaaaagaa tgagggaaag aaggatatat gtgtgtgtgt 141360
gtgtatgtgt gcgtgtgaat gcgtgcacac acgtgcacac gcatgtatga gagacagaga 141420
aacacaaata atctatttgt attgaaaagc aattttatag aaaaacctta atgcaaaaat 141480
caacagacat tttctaattt cttactaatt gtctgttaga ctgtcttagg tacgtattaa 141540
aatagcttca ttgctgtaag aaacttcttt ctagtccaat aaactatatt tctatgtgct 141600
gtatcagggc cctgttaaca ctgtgattat aacagtaata atcacagaca gccttgggaa 141660
agccactaaa cctctgtagg cctctttttc tccatctgta ttgagaaaaa taatgggatc 141720
tacctcacag aattgtttat gaggatcgaa tacaataatg cttgctctaa tacctcatat 141780
atagtaagtg accaacagat ggaccaatta aacaatagaa gtttattgaa catagttgtg 141840
ctgggtggtg tgctgcttta cctgtattat ctcttagtcc cgtaaggtct acgcagacct 141900
tccatatttg actgataaag ttcaaagagg tgaatttatt tgcctcagat tgtacagtca 141960
ggacctggca gggcagagat ttcagctcat gtgtttcagt ttagkttgtt gacttggaac 142020
agaattcact gtacctctga gtaaatttgg actattttga tcaactgtgt tggcagtaac 142080
tggccaccga gtgccttggt ggggtgcagg aaagctgtgg ggttctcatt tgtcttccag 142140
agatttctct tagctctcct gaaggatttt tgcagtttct ttaggcagtg gctctgtatg 142200
ttttcccaac tgaatcttcc ttttatccat aaaaatgttc cctcctgaaa ttttaggtga 142260
gttggaagta ggaacttggg aggtgatttt gctgctctta ctctcatttt ctattgagct 142320
aatttcctca tttccctgaa gtgcaatata gattatctga atctcatgca aatcctctct 142380
catccatccc taatcgtgct ttrgaatttg ttttgtacat aagttctcct tcatctcagt 142440
ttcctttggt tccccttatg aaagtcagtt ctaataagtg attttatgct ataggttttg 142500
acactccacg gagatatcag atacagaaaa acattgattg ccaatgatgg gacagctctt 142560
ggagttggct ttccaattgg cataactgtt gatcctgctc gtgggtgagt attcataaat 142620
ggcacgtgtc ttccatgcag cattgttctt gttaatgtca gggtctgaca aaatggaaga 142680
tttcaaattt aggacatctt ctgatttcat atgtcaacat ttgaaaaata atagatctca 142740
gtgagaaaga gaaatagctc tgacctatat ttaatgtgca ggatattgtt tgtattttgt 142800
cctatggtct tcaaatgaac aacactggat ttaaaattaa ttccaaacaa gcaagaattt 142860
taggaatttt aaaatagcat tataagaatt gacaatatat tctgactttg aaaggacacg 142920
gaaagctcta agggattatg taacatttgc aatagagctt gcaggatgag aagccttcta 142980
gtaggtggag aatgggttgc aaccaggcag tgactcttga ggccaaggga tccatgaagg 143040
cacagaagta tggcggcact tagcaggatt gtggggagag ccggaaccag aggcttagag 143100
tagggagctg ttgaccacat gggagataca acagataagg tcatttgggg acaaatcaag 143160
gagggccttt aatatcatgc taagaagttg aactttattc ttttgagtga taaggagcaa 143220
gtagggattt tttttaaaaa atttcaactt ttattttagt tatagggggc acatgtgcag 143280
gtttgttaca tgggtatatt gtacccagat agtgagcata gtacccrata gttagttttt 143340
caacccatgc cctcctccct tcctcccctc tctagtagtc cacagtgtct gttgttccca 143400
tgtgtatgtc catgtgtgct caatgtttag ctcccactta taagtcagaa catgtggtat 143460
ttggttttct cttcctagca aggaatyctg aggaagggag tgaaagaacc aaattygtgt 143520
tttagaaaaa ttggtcagga ttgrtgtgga gagaggccag ggccagggag accagttagg 143580
agaaaatggt cttaatggat gtaggctgga gtcctccggt ctgtttgatt ggctatttca 143640
ttctgttgat ctactatacc atattataaa ccagaataac aaattgtaaa atatgaacac 143700
tgatttttt tttaaagaga ttgtagcatc attccaagtg gattttggct taatgtttga 143760
aagttatcag attcttaggc ctagaagggc actgaagaag taatttgtat tagcgctctg 143820
tttcaaataa ggatgacatg gaaaccaaat ccaattttta aagggcacaa gaagcaaaca 143880
ttctattctg tgcctgctgg cttgtactag ttttcagtta ttctttctag aagaaggact 143940
gtcttaggtt cgaaattcta cttttgaaac tcaggctcac tcattatttg tttttcgttt 144000
atcagacatt tctgcattgt gtacctttgt tgggtggtgt gttagttaag atagctaact 144060
gttgaagcaa ataaactcct aaatatgtaa tggctcaaag aaaatagaaa ttttttttgtc 144120
ttttatatgg gcagtggggt ttgggcagaa gatgggagga agctctactc tacgtagtca 144180
ttcaggaccc aggctgatgg atgctctgcc atcttcagta ggaggcttcc taggtcattc 144240

tgagtatcaa gatctttcga gcagtaaagg aaagaacgtt cagaaatttg ctgggaggtt 144300
tttatgagcc aggcctacaa gtagtgcacg ccacttctgc tcacactcct taagctagaa 144360
ttgggtcaca tggccacagc taactgcacg gaaggacatg cagtccacct atttacccag 144420
agagaagagg aagacattaa ttttggcaag tggaggcagt ctctttcatg gggccatggt 144480
ggggagttca gagggtggat acaaagatta aagacctaat ttgcaacctt aaggatttat 144540
ggcttagtaa ggaggataag gcctgtgtat aaataacaat aacccagatt catataagat 144600
taagagccac aagagaggct aaaaaaattg ggatgatagt gctataaaga ggtgacattt 144660
cagcttggtg gaagagatat catttggact ggatcttaaa gcatacctag aatttcactg 144720
ggcagagcta gcttttaaga tatatcaggc gatatgaagg atggaaggtc aagagcaaag 144780
ggacagaaaa ttgagggttt gttcaagtga ctaagagcaa cccagttggg ttgggagaca 144840
attagaagag cttagaattt tgtcagagga cataggagga gaaacaagac agagacttga 144900
ggatctaata tcttggattc tcagtgaaga gaaagtcttg ataaagttgt gataaatgtt 144960
attgaaccag ttgttgcaga aaaatatctt tgtggatgat cactaataaa gagctgaggc 145020
agttacaggg tctctgatga tattcaagag aggatgttga atagagatag tagaagttaa 145080
aagaatggaa ggaggatgag gaaatgtgaa tactctttta agaattttgt attggaaagt 145140
tagagaaaga taaacttgta ggtcaaaatg taacaggaaa atgtctttca gaatagagaa 145200
acctgagtgt attctttagc agcagatgaa agatcaagga tgaagaaata attgattgag 145260
agtgaaagtt atggggaagg aattcgaaat ttatgaagta gaatgacttg aaatagtcaa 145320
tatgcggaac atgatataaa gtctgctagg gatgagaatc ctcagcttag attagggaac 145380
ttagattttt agtgaattca gaattcacga aagttttgtg ctatgtccag gaaactcttg 145440
gtaccctgaa atgggagagg agaaagaaaa aaaagggcag aaacccaggg ttggagatta 145500
gcttagacac aatgggaacc caaaagaata aataagaata ttgttgaaat ggttacatat 145560
gatgtccagg tgtagaagra ctggagggtt gggagctcag gcagggctta agggcaaaga 145620
acaagtttaa taggaaaagt taaagcaagg aagaaatgag agktttggt cgaagcagag 145680
catttcagag tttgagaact tagaggcgga gaagtttaga gttgaagatg aaattcaaag 145740
gacgggtata ttgatttggt ggtggaagag gtaggtgaat aaagactatt taaatgaagg 145800
ggtttaagga cttttcagaa aagaatgtag gagaattgtc tgttgaagat atagaaggag 145860
gtgcaatcaa aaggaattaa aagttgggtt caagtctaga acttacatct tcagtggaaa 145920
tggaaaacag cccttaatat attttaatac attttcatat atcatggatt tggcaatgct 145980
gtgtggtaat tatggttcat gtgtacctga tcgctgtgaa atagaaagaa aaaagaagtc 146040
ttccttaccc cataacagca tgataatgag attccactct cacagaaaag tgttactcat 146100
tatttctcct attttctgtg tcagttttca aaattctttg catttttcat cacagaaatc 146160
aggttaggta attaagtagc cggtcttgtg gtagatggtg atttggrgaa taattaaatg 146220
aggcctggta agtgatcagg gagtgtactt ggcagctttt tatattagct ttggccttca 146280
ctatgtactg aagatggagg gattattgat gtaggtttct tccttgtcat aagcttccca 146340
cacacctgac catgctaaaa gttcagctgc cagtgggata ccctagcttc ttattccaga 146400
caccatttta agtggcctct actccagtta tagctaggaa atataccgac attggtagaa 146460
cactggtgaa gtacccctcc acgttgtatg caacgagata ttgattttca gcctttgccc 146520
attgtattgt gagcatcttg aggacaagta atacacattg tcatttatgt cactgactca 146580
aatccacctt ctgttttgtt acatgctggt gtttttcatg gttgtaggaa gctgtactgg 146640
tcagaccaag gaactgacag tggggttcct gccaagatcg scagtgctaa catggatggc 146700
acatctgtga aaactctctt tactgggaac ctcgaacacc tggagtgtgt cactcttgac 146760
atcgaagagc agaaactcta ctgggcagtc actggaagag gagtggtatg agcacccttt 146820
cagtcttttg gtctttatgc tgagctggtg tagctgatgc tgagtgttct gagctgtcag 146880
gcagtggttc ttgaacaatc ttacttggta acttgtacca gtgtttcatt gccccttctc 146940
ccaataactt ctctcccttg cacgtacctc gcccctagct gaagtccagt tctttatagt 147000
atgtgcatag ttccctatag ggtaatgttt attaatttcc ccaccaacgt ttkttttttct 147060
tcaagataaa ttaattccat ttgtcatttc ttacttgtca tttcagagcc atttctttca 147120
tggtttagtg atttcagtgt ttttctttga aagtactctg ggttctccaa ttatagagaa 147180
tatacatata cctatatata tggagagaat atatatataa aaaatataga gtatgtatct 147240
atactatatg gtatatagaa tctatataga ttctatatat gatctatata gawtctatat 147300
atgatctata tagatataga atatatatta tagaatatag aatatatatt tatagaatac 147360
agaatatata tctattatat atagaatata gaatttatat atctgtatag gatataggta 147420
tattctatrt atctacctat gtgtgtgtgt atgtatgtat gtatctattt atttacgtag 147480
caaggttctg aactcagcat cccctcgtag ctacacattc ttctctaata ttttaacatg 147540
attaatgcac atgcgaaact ttctttagtg gtgattttca actccaaggt tgggttcatt 147600
atattctaca ataagaagca gaaactataa agtctcgttc actcattgaa ataggatttc 147660
accttcactg agctggggct aagcacatag acaatgctca ataataatta ttgatgaagc 147720
attgctttgg gtgctgaact gaatatatgc tagtcccttc cttgctattt aacagtagtt 147780
acttcagatc ctkgacattg atgcttttca taatattgtg cagtaggttt ggctttcagt 147840
tcattgtttg ttcaacaagt actaacttca ctccgaatat ggacctataa tggtggtaag 147900
ctttggagat taaaaagaag tgatgatgtg tgtgaaaaca ctttgcagag ttgggtgcat 147960
gtgtgcaatg acgaggaagc tcttgttaca tggtatggtt tctgtacaca catctgacag 148020
ggcacagctt ctaaatctac gtgcttgtta gtggtgtgac tctccaacct ttctcctagt 148080
gtagttccct tatttctcct tcactctcct ggtttaatca tcaccaaatg ctgcaatcca 148140

tcctcagcct gtcactcatg cccagatctt ttctgccacc tccaccattc tgagcaacct 148200
ctctctggcc ttgactaggc atggccttca gtggtgaagc ctgctttcat gttggagaca 148260
tgttttcttc ataaagccac agtcagcaag ttggatcacg gctcagcttg gagccttgcc 148320
ctgaggagta gctcccaaca cttctgtgag gttgctcagc taatctggtc ctggcctcca 148380
ctctctccac tctctcctcc argctcatgt ttcttatatt ctaaattcta gaactttgat 148440
cagtttcatc agcataacca ctcttgtaac tgctgggctc ccttttcagc catggcwgta 148500
aagccacact gtgtctctcg ccaataccca gcccagatcc tggcacagag caggcacttg 148560
aggcaggttt ttggagtgaa attaaaccag ctacatctac atttcatttt tcttccagaa 148620
gaagctgact acttgtcatt ttcccttagg gactttattc ttgtagttct tttccagtgt 148680
accaaagcta ttttgattaa agcttgttat ctgttcaaat ttaatggcac cattttggc 148740
cctgtcctgt cttgctgtcc tctgtggttg tttgggggca tatttccaat ctccattaca 148800
gaaattgtca gtgaaggtgt taaactcagg gtgagtcagc tcctgtgcaa tggcccacgc 148860
ttagatgttt gagtatatcc ttgaccagaa tatcacatgc agggactagt ggtttagctc 148920
ccttttcttc accgtgccac ctgaaaaggt tgactgactc atgtgagctc cgtcttcatt 148980
atcaatgaaa ggggcacagt gacattttcc tgacctgctg cttggtgtsg ttgtgatgat 149040
caaatcagaa aatagaagtg aaaaatctct gtaagggata gagggctgta taaatgtgag 149100
acattataat taggagaata ttagtgttta aatgttcaaa attttcacta tgaatccatg 149160
aaactaatga aaattccaat cctttagatt gaaagaggaa acgtggatgg aacagatcgr 149220
atgatcctgg tacaccagct ttcccacccc tggggaattg cagtccatga ttctttcctt 149280
tattatactg atgaacagta tgaggtcatt gaaagagttg ataaggccac tggggccaac 149340
aaaatagtct tgagagataa tgttccaaat ctgaggggtc ttcaagttta tcacaracgc 149400
agtaagtatt tgtcaytgaa atacattcat gggtgtataa tgcatattca cacataactc 149460
acatttgtaa gcacacaccc acacacagtt tcacgtacat acacgtgcat acaaattgaa 149520
gttacctgaa atatttaaaa aatgataatg aagtcttaaa catggttaag tgccaagggc 149580
taatttggca tctgaaaggc cagattgact tcagagtaag tttattccct ttctcttccc 149640
attactttca attccttact ttgcttttac ttcatagaac tccctgtttt ctattgtttg 149700
tgttacttat tagaatataa cctctgtacg ggcaggcatt ttgtctgtct tgtttgctgc 149760
tcaatactcg gtgattagaa tagtgcttgg cacataaaag gtgctcaggg catatgagtt 149820
ggatgcctgc tgggaaagtg ctaatgggat ggaattttta gtcttaaaaa gaatgctttt 149880
ggatgttgcc tatttcaaca tttttttcaa agataatcta atttctgatt tacccccttta 149940
aattagtggt atgatacagg tattattttt tgatgtattt tatagctttc gtcttcagcc 150000
aaagatgatc aaacaatttg tttcctgtcc tataacctaa gtttgtcact aggtattttt 150060
ttaactgcat gtgaaagaaa cacatgcaat agaaattaat tttttattac tataaagaat 150120
attctttttt ttttatttttt ccataggttt ttggggtaca ggtggtgttt ggttacatga 150180
gtaagttctt tagtggtgat ttgtgagatt ttggtgcacc catcacctga gcaatataca 150240
ctgcacccta tttgtagtct tttatccctc gccccccctcc caccccttccc ccaagtcccc 150300
aaagtccatt gtatcattct taggcctttg tgtcctcata gcttagctcc cacataccag 150360
tgagaacatg cgatgtttgg ttttccattc ctgagttact tcactttgaa taatagtctc 150420
cagtttcttc caagtcactg ggaatgccat taattccagg actattcttt aaatcttatt 150480
tcatatattt aaaaaaaatc acattattga tcatgtaact gaacatatta ttttaagtgc 150540
cagttcatag gcaaattatg agcagattta tatactgacc tccctaatcc tcgcatgatt 150600
tgtagaagaa aacaagtgaa gccccattct ctaactatta tacaatagtt gggttactgg 150660
tttcatacct ttaggtgtta ttgtataagc tctagtctct ccgatgttgt ttttagattg 150720
ctaactcagc tactatatgt tggttattaa tttttagaat aaattatttg gtgacccaat 150780
taaagaaatt tgagatgggg tggcragtag ctaggatcaa aagttacaaa tggattttgt 150840
tttcatttag atgcygccga atcctcaaat ggctgtagca acaacatgaa tgcctgtcag 150900
cagatttgcc tgcctrtacc aggaggattg ttttcctgcg cctgtgccac tggatttaaa 150960
ctcaatcctg ataatcggtc ctgctctcca tataactctt tcaytgttgt ttcaatgctg 151020
tctgcaatca gaggctttag cttggaattg tcagatcatt cagaaaccat ggtgccrgtg 151080
gcaggccaag gtatgccaac tccaatataa gtaagatttg acttcatctg gcaccaggtt 151140
gaaatccctg gtgccatgaa aacatttctt catgtgtgga ttcagtgcat aatgaagctt 151200
tcctttccct ttaaatcaac tggcacagcc taaagtgttt ttcaaacttt agtgtgtctc 151260
agaatcacct ggagggctca cgccaacaca gctccagacc tcgtccccag atttttctga 151320
ttttgtagtc tagggtaggg ccagagaatc tgcactccta ataagctccc agggcatgct 151380
gacggtgctg gcccatggat cacgctaaga accacaggcc cagagcaata tagaatgtag 151440
gatgggtttg caagaagtac tacagagttg gtgttccaaa gaactgtgcc ctatttctga 151500
ttattaatgg agatttatgg tagaaggtat actactattt aatatggtaa tgaaatagtc 151560
cacaaatatg atttattaat atatatttgg tgaattgaag caaaagagtt cacagtgtca 151620
stccctcttt agtaatcata tttttgcagc actttgtgct tacatactgt gaatgtatga 151680
aacgatcact tgcttcctag atgagccaag gtttttaggt ataccttagc acaagaggaa 151740
ctaagagttt tctaacatcg ctaggagaat gtcacaggct aaagagagaa atagagggta 151800
gaaaggaagg aaaaaaggat gaagtsaatg aaggggttgt agagatggtc agaaaataca 151860
gaaatgcacc tggagaaggg aatcagagag cttccagtcc cacacgtcct cctgcctgat 151920
ggtcatgttc acgtggaccc atgactcatc tttgtttttc catatctaaa aagttatgga 151980
tctaagttat catcttgtac agatatgaca aattcaatag ttttttttctc ccagcttttc 152040

attaaaaaaa tgttcaaaca cagaaacgtt gaaagattta ggaaatatcc ttatacccttt 152100
taccaagatt taacagttgt taacatttct tcacatttga gctctcaatt tgtatgtgtg 152160
tgtgtgtaca tgcatatgca ttcacattca ttttttatga acctttaaa aataaatttt 152220
aataccatgc cactttaccc ctacatatgt tagcatacag tttcaaaggg cattatgaaa 152280
tattcataat catatttctc cagttggcct cacaatattt tatatatagc tgttttgttc 152340
catccaagat ctaatcaaga ttcatgcact gcactgggaa tatctcatta gtttcttcca 152400
gtttggagta gttgcctcta gctttttgct atgacattga tgttttaaag aggcagacct 152460
gttgtctttg agaatcccac actgaggatt tgtctgaata tttagtctgt ctttcatttt 152520
ttaccctgca gttctcatga aatggaagtt aggtctaatt gcttgattag atcaaggtta 152580
aatacattta gcaataatac tttataggtt atgctgtgtt agttgataca gaatcttatt 152640
aggaagaaca taatgtcagc ttgccctgct cttagtggca tttgagtttg atcacttggt 152700
taaggtggtc actgctacac tgctgctttt taaagctgta ttttttttcc ttcttaattt 152760
tggtggaatc tatgcaatca cacttaggcc ctgtgaatgt cttggctccc aagcaccttt 152820
tacccattgg ttttggcagc catggatgat ccttgtttga aatgattatt taatcgagga 152880
ttgcaaaatg gtgattttct tattttagca ttccctttac atttgttaga taatattctt 152940
ctataaagga aagctcttcg tgtctccccg gtttactttt taaataattt attattatta 153000
tgggctcaaa tttttatttt ttaaattcag tgtgttacag tcaattactg taatccttct 153060
tttgatgttt tagtggatcc attttggcca gggagaacct cttcaagtgg cgacctgtat 153120
atttctgtgt atgccttgtt tcttggtaca ataagatgtt tcacactcac ttcgtacctt 153180
ccctgcctaa acctataatc aacatttctc ccgggagcca gagctcctta ttgtgggaaa 153240
gagtagaaac caagatgtgg gtctgctcac tgcaactggg aaaaaagggt ttcattttgt 153300
aatggggaga tgctcagagc agggggttgg gaatgagggt ttgagaggaa gggcagacat 153360
ttaaaagttc taatttcagt gacagcattt tttaatgatc ttttcttaac ttccaggacg 153420
aaacgcactg catgtggatg tggatgtgtc ctctggcttt atttattggt gtgattttag 153480
cagctcagtg gcatctgata atgcgatccg tagaattaaa ccagatggat cttctctgat 153540
gaacattgtg acacatggaa taggagaaaa tggagtccgg ggtattgcag tggattgggt 153600
agcaggtatg taagctatat ggtgatttta atatgtttgc atctctgtca tcttatttta 153660
tgctagaaag tttagcctaa ctccatgtgc tacaggtttg tttttctaga caattattaa 153720
gaccatttaa gatacattga atctagatta agctacgtgt ctatttgata aatgatacgg 153780
tgtttcagtt tacagattta taacaaatta atccttatca ttttcttctg ttattaacat 153840
aatctggaga caaaagtggc taaaatatta aattatgtgg atttgttttt tttacactta 153900
gatttgcacc tgatttctgc attagaaatt ttctaaattt tcaagagaaa gagatataaa 153960
aatataaact atggaacagc attcatttgc tttgaagctg agcaatttta gttgccaaat 154020
tcttaattgc ttccttttat tcatatataa aaatccctta gatcatgaga tattttatta 154080
gtaatttttt taaatgcctg gtccagtatt atattaactt agttgtattt attcatgcac 154140
ataagcttga ataacccctc atttttatca ctcatctgag taaaaatacc actcataatt 154200
agtggtatta tatgttttgg aatataatcc aattctacat aaaatcagta tcattgaatc 154260
aagcttggtg agtaggcatc acttagaaat attagcatgt aggcagggcg cagtggctca 154320
tgcctgtaat cccagcactt taggaggctg aggcaggcgg atcacctgag gtcaagagtt 154380
cgagaccagc ctgaccaaca tggtgaaacc ccatctctac taaaaacaca aaarttaacc 154440
aggcatggtg gcgtacgcct gtaatcccag ctactcagga gcctgaggca ggagaatctc 154500
ttgaagccgg gaggtggagg ttgcagtggg ccgagattaa gccactgcca tcaagcctgg 154560
gtgacagact gagactctgt ctcgaattaa aaaaaaattt aaaaaaagga aatataagca 154620
tgtattatga aaatctaagt actataataa gagtttattg caaaaagtaa atatggaagt 154680
atggttaaat aaagctttaa ttgggttcct aactcccgtt cctgaataga aattactatt 154740
tctgagggta tagataaagc agtagtcagc aaactatggc ccgtgcgtca aatgcagcct 154800
gttgcctgtt tttgtaaata aagttttatt gtaacacagc tatgcccatt tatttgtgta 154860
ttgtctatgg ctgctttcat gttacagtgg cagtgttgag tacttgtgaa accatatgct 154920
ctgcaaagcc taaaatattt attatgtggc cctttacaga aaaagtttgc caaccctgga 154980
ttawaggatt ggaaatgagc aaatgcatac atagcaagta gagttaggta atgaaaaaat 155040
gtatcagtaa catatttcac attggcctsa tttctctaga ggtggtttga atcagatata 155100
ggaacaaaat atgtgtgtct tggtagtagc attgatagtt caacaacaga ctttcaacta 155160
catgaaatca ataatttgtg gtcattctct acttattata ctatcttcat aaagttatct 155220
ttttattcta gcatgtacat aaggcccaaa gggaaatgga cttttggtca cttttagaag 155280
gtccatggga tgaaaacacc tacattagtt agaaagacta aggaaaaact tcatgttaac 155340
cttaagttca aagaccattt gataacatta ataacaacct gagatgctgc tggtgctccc 155400
tctttgctac ttttatcaca ttgggatgga agttgtgcta tgaaaatgta tatttagagt 155460
gtttcaagta ggtattaagc atttagagct tcagatagaa aaggagggac attctggaaa 155520
atataccttt cagtagaaag tgggttatga tgttgctatg aattctaatc tactttagaa 155580
gctgaagata ggcactttct ctctaaattt gaagacacaa tctctataat tcctaggagt 155640
aagaacttat ttttctaagc ctagactggg acactatcat cttggaaaag acaacatata 155700
gtgacccaga cttcaacctt atatattttg ttctgaattt gtaaagttct ccctttttt 155760
cttcttggtt ctccattgat cagcrtgcac tttcattttt cccataggaa mtctttattt 155820
caccaatgcc tttgtttctg aaacactgat agaagttctg cggatcaata ctacttaccg 155880
ccgtgttctt cttaaagtca cagtggacat gcctaggcat attgttgtag atcccaagaa 155940

cagatacctc ttctgggctg actatgggca gagaccaaag attgagcgtt ctttccttga 156000
ctgtaccaat cgaacagtgc ttgtgtcaga gggcattgtc acaccacggg gcttggcagt 156060
ggaccgaagt gatggctacg tttattgggt tgatgaytct ttagatataa ttgcaaggat 156120
tcgtatcaat ggagagaact ctgaagtrat tcgttatggc agtcgttacc caactcctta 156180
tggcatcrct gtttttgaaa attctatcat atgggtagat aggaatttga aaaagatctt 156240
ccaagccagc aaggaaccag agaacacaga gccacccaca gtgataagag ayaatatcaa 156300
ctggctaaga gatgtgacca tctttgacaa gcaagtccag ccccggtcac cagcagaggt 156360
caacaacaac ccttgcttgg aaaacaatgg tgggtgctct catctctgct ttgctctgcc 156420
tggattgcac accccaaaat gtgactgtgc ctttgggacc ctgcaaagtg atggcaagaa 156480
ttgtgccatt tcaacagaaa atttcctcat ctttgccttg tctaattcct tgagaagctt 156540
acacttggac cctgaaaacc atagcccacc tttccaaaca ataaatgtgg raagaactgt 156600
catgtctcta gactatgaca gtgtaagtga tagaatctac ttcacacaaa atttagcctc 156660
tggagttgga cagatttcct atgccaccct gtcttcaggg atccatactc caactgtcat 156720
tgcttcaggt aagtgcactc caggtgctgc ttgtcctgca agtagacaca atggggtcaa 156780
cacacatgga tgactgagtg tttctaatgc atatgagact ctaatgtctt tgtgtgtrct 156840
tgtgtgtgtk tytgcctgta tgtgtccagg tatagggact gctgatggca ttgcctttga 156900
ctggattact agaagaattt attacagtga ctacctcaac cagatgatta attccatggc 156960
tgaagatggg tctaaccgca ctgtgatagc ccgcgttcca aaaccaagag caattgtgtt 157020
agatccctgc caagggtatg ccatcatctt ccttgttata tttctgtctg cttatttctg 157080
gaaaaaatgg ggcctgaaat tatgttcata gatagccaat gtgttatggg cttataaaac 157140
tatggctaca gattcaaaaa tgaaagcata ttgagtgatt ttacgtggga aggagggtgc 157200
agcgcatagc tccctttgat ggcagaaagg ttggcaacat actaggaagt caacaccctg 157260
acttactaga tctcctttgg acaagttgtg taagtagaaa tgaagtttct tttgccatgt 157320
tactggcaat ttgcaattaa agaatattgt cctttttttt ttttttaaag gactatgagg 157380
ttccctgtga attaattatt gactcctttt gtatgactag gtacctgtac tgggctgact 157440
gggatacaca tgccaaaatc gagagagcca cattgggagg aaacttccgc gtacccattg 157500
tgaacagcag tctggtcatg cccagtgggc tgactctgga ctatgaagag gaccttctct 157560
actgggtgga tgctagtctg taggtgtctc tggttactca tgtgggtgtt aagaagaggt 157620
ttttcttcca tttccaaaga agagggattt gcatcatgtg atgaaaatat agcatgccag 157680
atagacattg ccagaatata gaatcacagt tttaggaact atgtttatat tggaacttgg 157740
tgaacatact gtgaaaattt atctatatca tgcattgaat aattatgaac taaaagacat 157800
ctaaagatgc attgctaaat atatctataa tttcagctat aattataaat gtattttctc 157860
aatttagaat tacaaatgaa attactcaac ttacattctg caggccctag gtaactgcta 157920
taaaatctga atgactttta aatgccaatt gatattatgt ttttttctgg gctttagcat 157980
tcaatgtctt ttagaaaatt cttttcttaa aaaaaaaaaa agaaaattct tttcttcagt 158040
ctttgacttt ttgtcatctt ttcaaataga ccctttcttc tctggcaagc ttctcctcag 158100
cgcatttctt aatattttcc ttttgtcaac tctaattttg tatgtaactt ctccaagtac 158160
cccccatatg tctcacattc cagtcatcct aatggaatag ttgaagggat gaaatgattt 158220
tgtttattat ggctggtgtc tacatatcgg gaatcttaat ttttcttgca tatttctttg 158280
gaattttagt cttttgatgc caagacctaa cctcctgatc ttttctttat tctcctattt 158340
gaaacaaagc agtgatgctt tgagtctaag cttggattat tctaggtaaa cacctcaagg 158400
tactcaataa acatcaaatt gaaaaagtca ctaaggaagt gggatggaaa agttattgtt 158460
ttattgagag tctgctatgt gcttaacact gagttccatg cattacatgg attatttcat 158520
gttttcctgt ttctaatatc aacctgattc cttttgtagg attactattc atatttggaa 158580
gtcaatgatt ttatataggc tattgtttga taagcaaaca agacctccca tcaccagaag 158640
aaacatttcc agctgccata tgccccattt gaaaagaaag tttgcagctt gtgtaaacaa 158700
tgatgaggcg catgcattgg gctgccagtt gaaaacttaa ctcacttgag atttcaactt 158760
ctaaattttt ttttgcttca ttttaggcag aggattgaac gcagcactct gacgggcgtg 158820
gatcgtgaag tcattgtcaa tgcagccgtt catgcttttg gcttgactct ctatggccag 158880
tatatttact ggactgactt gtacacacaa agaatttacc gagctaacaa atatgacggg 158940
tcaggtcaga ttgcaatgac cacaratttg ctctcccagc ccaggggart caacactgtt 159000
gtgaagaacc agaaacaaca gtgtaacaat ccttgtgaac agtttaatgg gggctgcagc 159060
catatctgtg caccaggtaa ggcactgacc atgaaaatta gaacatggag aataatgatc 159120
acaataccaa ttggtaagga aagctgaagt tctcacagga gaaaaaattc aaattctcct 159180
tgatgtcagg gtaatttatg aaacagacct ggggctatat tttgagagga agacttggca 159240
ggcttctttt ctaatctata tggagccctt ttatgaaagc attttctttt attttatttt 159300
tgagacggag tctcactctg tcgcccaggc tggagtgcag tggcgggatc tcagctcact 159360
gcaacctcca cctcctgggt tcatgccatt ctcctgcttc agcctcccta gtagctggga 159420
ctacaggcac acgacgtgtc cagctaattt ttgtattttt agtagagacg gggcttcacc 159480
atgttggcca ggctagtttc aaactcttgg cctcaagaga ttgcccacct cggcctccca 159540
aaatgctggg attacaggcg tgagccacag cactcagcct atgaaggcat tttaaataca 159600
agcttgatgg agttagaaag aaagatgaag gccttggctg ccctacttca tgtcttgact 159660
aagaattctg tcaatgagct ggccttcctt ataaaaggat ttacattttc tgcttaagag 159720
gtattattta tagtttgaaa tatttctggt gatatttgcg ggtgggatca tatgtgcttc 159780
attgtgcatt ttataaagaa caacaaattc acgggaagat gtgccttttg atgttgttgc 159840

tttgcaaatt ttgctgagaa gagtcgttga tatttcctgt tgtttagaag gaatcggcac 159900
atttattaga aattggtgat tgctcttctt gatggaaaag tgactcagaa tatagttaaa 159960
aggttaatgg gcagaacttc catggcgctt cttagggagc atttaatgta gaagctgttg 160020
caagtgctat tgtggagggg tcaatgtgaa csgtggctgc atccatcttt tacttcttct 160080
gggattatct ttcttcaggt ccaaatggtg ccgagtgcca gtgtccacat gagggcaact 160140
ggtatttggc caacaacagg aagcactgca ttgtggacaa tggtgaacga tgtggtgcat 160200
cttccttcac ctgctccaat gggcgctgca tctcggaaga gtggaagtgt gataatgaca 160260
acgactgtgg ggatggcagt gatgagatgg aaagtgtctg tggtgagttg gactcttggc 160320
gcttttggta ggagctaatg gcatcttgat gtcaagtgtt tggtatggaa tcctgctrtg 160380
tgtgaatgtg tttgaaatgt gtgcctaggc atcctggtag agctgaaaaa tgtttcctct 160440
gataatccag actgtttctg ttaaatcacc tctgtagtgg ttaagagcac aagcacaatc 160500
atcatcctgg tgatcgcatt tgtaatctgt atagacctgg gaaagttact taatatctca 160560
agcctcagac atctcatctg taaaatggag ctactactag ggttcttgyg aggagtaaga 160620
gaaacaatat gtaaaaatcc cttagcatga ggcatggtgc aagctaagtc tagcttagct 160680
tgggactaag gaaacgtatc attttaccaa ttttcrtagc acaaaggtca ttatttcaaa 160740
aattttatga aaataacttc caatcctcag cttccatctg aatagagtga ataaaacaca 160800
gtggactttc tcagggagtt ctgaggttgg ttacctttc ctagcagact gtgatagggg 160860
ctaggagttt ttattttcct gaaataaact ataattgcat gctttttgtg attgagataa 160920
attgagatta tagagaaaca gaatgacttt gatttgtgct taaattactt gatttgtgcc 160980
taaaacaatt ttaaaaatgt atacaacata ttttgcttaa tctaactaat taaaagtgtt 161040
atctcacttt gcatgcagtc cattttgcag cgtttttttgc cttggaaggt aaattcaaag 161100
tgtctctttt atttaattrt atctttttaa aaattaggat aatgttttaa tcaagagggt 161160
ttgttctcat gtttttcctg ttcttagcac ttcacacctg ctcaccgaca gccttcacct 161220
gtgccaatgg gcgatgtgtc caatactctt accgctgtga ttactacaat gactgtggtg 161280
atggcagtga tgaggcaggg tgcctgttca gggactgcaa tgccaccacg gagtttatgt 161340
gcaataacag aaggtgcata cctcgtgagt ttatctgcaa tggtgtagac aactgccatg 161400
ataataacac ttcagatgag aaaaattgcc gtaagtttat cttaagtgct tattgtgatt 161460
ttgggtctga agtcttggat cacaggagat gaaattatta tataaaaaaa aggctttcca 161520
aaaatraaaa ccctaagtat ttatctaaaa cgtaaatttt tggctaggcg cggtagcaag 161580
tatcaacaaa taccaatctt gtttcatttt tctctccttt tttctagtat tttaaagtga 161640
ctcctagtcm tgcacttcac tgataacatt ttggaaaata actaccatgc cattataayg 161700
cctggcaaaa tcaaaagtgc ttactaaata tccctgagta cctagtccat gttcaaattt 161760
tgtcacttat ccccaaaatg tatttttact gttctctgtt caagttaggg ttcagatgag 161820
atctacaact gattttgatt gttatmattc ttcaatctct tttatgccac aacacttccc 161880
acttttaat gtcattgatt cattagaaag attaggtgat ttgtcctgta gaatatctca 161940
cattctggac ttgactaatt gcataattga tccatttaat ttatcttatc cctcttattt 162000
cctatgaact ggtatgtaga cctagagttt tgatcataac aggtgcaatt ctttgggtaa 162060
gagtatttca gaggtggagc tgtgcctttc ctgttgcatc accttatgag gcacatgatg 162120
ttttgttgcc ccactttaag tggattctgg tgtcagcctg aatcatctct tatgaagctc 162180
ccatcatcct ttcacccagt ggttttagca tccatcggtg gttgttccgt aaacccatta 162240
tttctttaag agttatgaat gggctcttta gaattctagt gttcctgccg catttattag 162300
ctgaagtttg ataaagaaga catttccctt accagctttt gttggtaatt agaatctaca 162360
ggataaatac cttttgcttg tcaattttca gagtaatgag ttggtgacaa aggagaatta 162420
acttttgtt tagtttagtt tagtttagta ttatattgaa ctctttgatc ttcatgtatt 162480
tgatgagttt taatacagtg ctgtcaactg ttttttcttg gtgcccagtt gtccaaactt 162540
aggccaatgg gagtccttaa cttgaatttt ctgttctttg gcatgacccc aatccatctt 162600
cttatagctc aagcttgtct tatatttcct gtcccagtcc tggaattagc cacttatcca 162660
aggagacctc attccctttg tggtacttag aaattatcac agggttgagt tgctcattcc 162720
tacttagctt tcattgcttc tagtcctttt caatggtcag agctaggaaa tacagttttt 162780
aaggaaaaaa aatttttttа ttttttttgag atggagtctt gctctatcgc ccaggctgga 162840
gtgcagtgac gcgatctcag ctcactgcaa gctctgcctc ccgggttcac gccattctcc 162900
tgcctcagcc tcccgggtag ctgggactac aggcacccgc caccatgcct ggctaatttt 162960
ttgtattttt tagtagagac gaggtttcac catgttagcc aggatggtct cgatctcctg 163020
acctcatgat ccgcccacct tggcctccca aagtgctggg attacaggcg tgagccactg 163080
cacccggcca gaaaaaattt ttattgatat ttcccattga aatttaagat tacaggttgt 163140
ttacatttta gattttataa tgacatctct tcttatgctt aaaatcatag tttctcttga 163200
catttagttg ttttattata tagtaatttc aaaatgccta taataatttc aacattatta 163260
taaccactca aagaatacta ttaacaataa gtctactaag tgcgagattc ttcttgcttt 163320
ttagattatg tcccactaga gatatgcagt caaaggtatg actttaaaga tatttggaat 163380
ttttttttct gcagggttat gctatcaacc tgatatatag ttagctttat ctattgctgt 163440
ttccaaattt tattttattt tattgatttt atttgtacaa aatagcatac atagttccaa 163500
agttaaaact acatgacgag gtgcatttat agaagtcctt catttcttcc tctccttttct 163560
gcttcctctg tgctcttctc agtctatcca gagagatgac aatttttgtt agtttatctt 163620
ttctttgttg ttattgtttt taatataagc atctctctct tgctacacac acacacatac 163680
acttatatcg tccttttttct tacacaaaag ttagcctact gttttgaatc ttgctttctt 163740

actattaaca atatatcctg aagattatac tgtcattact tatcagtata tagaaatctt 163800
ctttattcct ttaatagcta catattactc cattgtgtgg aaatgccata gtttatttta 163860
ccaagagttg gaactcttgt tgatgctatt aattaatgaa aacagatgat ttaagttaca 163920
aaccagtgtc tcctctccct tctccccagt atcagctgga aatatgtttt tttactacag 163980
aatctatagg taacataagt atcatggatc ctgcctttct gatggctttg aaaatgccgc 164040
ccttccagtg gtttgagttc cacaatagat gtgttagcac ggatactgtt cataatacat 164100
atttggtgga tatattccta atatttatct ggttgycttt ttcaagctga tcgcacttgc 164160
cagtctggat acacaaaatg tcataattca aatatttgta ttcctcgcgt ttatttgtgt 164220
gacggagaca atgactgtgg agataacagt gatgaaaacc ctacttattg cagtgagtaa 164280
gataaaactg ctttctttct atcrttccag agrtgcatgt tgtgagctaa tacaaagata 164340
tgaagcgtgg gtattcgggc tgatttcaat tgtcatttca cattgacctt ctaagtagag 164400
gtggtaggca gttgctttca tatgtgattg caggggtatg agaaactctt tctctctgtt 164460
ccctggctag aattcccaga ccctgaatat ttcttccaga gatctgctac tattggagag 164520
ccatttctcc cagtgttgaa agccttttgc cttcatgtac ttaggcagaa tttgcccgtt 164580
aagcccttat aatttactct taatattatt atagtggcca tcagtaactg aaaattattt 164640
ttttttcaga cagtctcact ctgtcacctg ggctgtagtg tagtggtgtg atcacagctc 164700
accgcagcct ctgcctcctg tgctcaagcc atcctcccat ctcagcctcc tgagtagctg 164760
ggattacgtg catgtgacac catgcccagc taatttttgt atttttttgta gatatggggt 164820
ttctctgtgt tacccaggct ggtctggaac tcttgggctc aagcgatcca cccatctcag 164880
cctcccaaag tgctgggatt acaagtatga gccaccgtgc ctgaccagta actgaaagta 164940
tctttatatc ccctagatac gttggaattt cagaaatctc tatttcgtat ttagcaattt 165000
ggttcattca aacaatttcc tgtatttata gctcaaatta aaaggccttt cttaagtttg 165060
ataactttga gactattagt gtaaatagat acataattta aggatttagt gattggactt 165120
ccctgttctg tgtatatgta gttaaactct tgtcactggc ccctcccaag gaaatcaaag 165180
ggcatcataa ttatttgtca ccaaattagg gtacagcaca ggaagaggaa tctgttgtaa 165240
taacagcagc acaaggaagc agaattcagg ttgcagccac cagatagggc tagacagata 165300
ggaattattg ctgacttttc agggacctct gcttccattg tcagttctcc cctggcaaat 165360
catcagatat caggggccaa agcaaaacgg ccttatagac cagaagaatt acaagacttt 165420
aattagatgt gcacccacat aacaatttgg aaaatgcata taaccagagc tacctaaaat 165480
tactsgagaa aagagtcaat gttcaaacat aggcagagtt tcccacttac tcaactaaaa 165540
gtctggtatt ccaaggatga atacgaagat aactttgcca actttctaga gttattatct 165600
aacatagcta aaaggttgtg tgtggagcga gcttagatat gatcacatta ttgttttgct 165660
tttaattatc attgcaatgg aatttattta atcttacatt atagtagaaa aaataaaacc 165720
aagacttata atttgtgatt tcatttatca caaagatagt tctttggtat ttctaacaaa 165780
tacaattttt ttttttgat ttctggaatc tagaaaaaca aattggggaa ttggggcagg 165840
attgacttcc ttctgtctcc catacttctt cctccccaca gaaagcttac acaagcatcc 165900
attttccagg ctcagtcttc ctttttggt aactattatc tagctcagag atagaggcag 165960
attgttaaga ctgatgggaa catgcttrtg ttttgctcat gggttttatc ttctttccct 166020
cctgcagcca ctcacacgtg cagcagcagt gagttccaat gcncatctgg gcgctgtatt 166080
cctcaacatt ggtattgtga tcaagaaaca gattgttttg atgcctctga tgaacctgcc 166140
tcttgtggta agagagtaag caagcatgaa aaacatcacg atgcagctag acaacttcag 166200
tctcttccaa ctgcttcaaa tacagaccag ggtcatggct gctgaatgct tggacttcct 166260
gtcccagctt tcatctggaa tgctgacacc gctcagcgga tattcattaa gacctgttag 166320
tggagagcac tgtgtgggga gctgatcagg atacggaagc tgctgattga tgctgataaa 166380
atgaaattat attggtgatg cacctaatac agtgcttagc tggtagaact taattttagt 166440
tggctctcaa ttgaagtttc tgaatttggt tgagtgctgg cccagaaagc tgtcagagga 166500
cctaaaagtg attggagtca tatacatggg gaaggagtat attaggagca tgcatcctct 166560
tcctgttctc tctctgtgcc agtttatgag cacaagaggc ccaagaagtt gcaggagcct 166620
ttggttgtat tcctggggac agttatgccc tgtttacatt tggaggctgc tatttgcctt 166680
cacaaattct aatctatatc catgcacatt ttttacataa ttgtaaaaat ataaaaatac 166740
aatcttctac attgctttaa aaaacctgtc aataaatcat attgctatat aggagtcaga 166800
aaactatggc tgtggccagt tgcctgtctt tatagatagc attttactca aatgcagcca 166860
catatggctg ctgtccctct actatggcca cgtcctgtag gtgcaacaga gaccataggg 166920
cctgtaagcc taaaatattt actatctagt taaaaagttt gctcgtcctt gtcttcatac 166980
tgccttttaa tgactataat attccattga gtggttatag tatcatcaaa ttaactgcct 167040
ctattattaa gcattaggtt gcttttattt tattcctcta tagtatatat cattgcagta 167100
aatattaaca tcgtatttaa aacattttat tttcaggata ttttcttagg atcattagta 167160
tagttttata gctgaagtca aactattttc aattccagtt ttctctcagg tttaaattct 167220
gtgttgaaga gtggtatttg gagtgcttca ctaagttctt tttccccaac actgaaagtt 167280
ttatagaaag caaagggcac atagagtttt gaggacctgt aaaggaaata actaataact 167340
gctggatgag tagaatagtc ttagagattg tttcaaatgt atgaattatt ggttcaaata 167400
tatgaataat taatatgagt ttttaaactt ctctatggta acaaaagcca tagtaatagc 167460
agtgagtacc aatgacctga tatatttaaa taaaaataag cacataatmt atatatgaat 167520
atatcctcat tgtagtaaag taataatatt cagaaatata ttttaaagaa ataatacgat 167580
gtacaaaaaa gtaaaattta catttttca tccttctcca atcccctcac tcctcaaagg 167640

taatcactat taaaaggttg agtgtgaatt tgacttactt ttatctttta tatatcttac 167700
tttactttta tatatcttga tatatagatt ttaaaaaaac agatggagtc ttactataca 167760
tattttctgc aattagcttt tatttttaa gcttaacatc atgtcagcaa atacagacca 167820
gcctcattcc tgtacactgc caaagaatat tttaaaatgc gaatggtcca tgtattttta 167880
tccttttcct agtggttgga catttaggtt gtttccattt tttcactatg aaaaacagtg 167940
tcagggtgaa catcctttgt gcacatgtgg aaagatcctt atggtctaga tgtccagaaa 168000
tggtgctgct gtatcaaagg agatatgtct cttcaaaaaa tctggatcag gccaggcgcg 168060
gtggctcacg cctgtaatcc tagcgctttg ggaggccaag gcaggcggat cacaaggtca 168120
agagatcgag accatcctgg ccaacatggt gaaacctgtc tctactaaaa acacaagaat 168180
tagccgggcg cggtggcaca cgcctgtaat cccagctact caggcaggag aatcacttga 168240
acctgggagg cggaggttgc agtgagccga gatcgcacca ctgcactcca gcctggccac 168300
agagtgagac tctgtctcca aaaaaaaaaa aaaaaaaaaa agtctggatc aatgtacaca 168360
cttttcatag cagcttctga aagagcctgt ttcttgttac tgttatgata taggctgtgt 168420
ctttatcagt tgcaactata ctttctcttg ccttaggcta attccagggt cccctgggtt 168480
tgggagccta tgacaccttc attagttaaa taggaacatg tggggttagg gttagagcat 168540
ctgaatcagt gatggctaat ttgaagtaga agagtgactt attttaattc agtatttatt 168600
gaacagtggt gttctaggaa cttttgggct gtgtcagtga ataagacaac aatccctacc 168660
cacatgragc taatattcta aagaggggag acaggcaacc aatcagtaaa ttgtctagta 168720
tgttgaaagg tggtgctaag tgttatggaa agaaggaaag ggagcaagga agcgggcatg 168780
gggagtgcag gcgrggggag actttgcaca aaacaaaatg gttttggatg aaaagtagat 168840
tttaaaatag aaacatgtga aatagtaggt aattcatatc tttcctggga aaagaagtgt 168900
tctttctcta ccatacacat aagggaatat tgtatctcat tttagtcacc aaagataatt 168960
agggctttgc actgtcagtt gactactttt acctcaaact gttggtcgct ggtactagtc 169020
ttattggagg actaccctag atgtatataa ttaaataatg ctctgtttca ggtttttctag 169080
acaacccatg ctacarccag cttgtctcca gattcctgga ctgtaaacca ctttttttca 169140
ctgagaatgc tattgatctt ttcaggtcac tctgagcgaa catgcctagc tgatgagttc 169200
aagtgtgatg gtgggaggtg catcccaagc gaatggatct gtgacggtga taatgactgt 169260
ggggatatga gtgacgagga taaaaggcac cagtgtcgta agtgaagcca attaattcct 169320
ctgcagagtc acattccagg gaaacacagt agagttgttt ttctgtgttt ggagagtatg 169380
attgcagatt tctctgtaat tgaatggaca ctgatagaat gttacctttg tttctccatg 169440
ctgggagtgt ttgatatcat ccacttaaat gcttcagagt gatgaaaaat gactttatgt 169500
ttactttctt tctcttacat ttggctaatg gacataatgt cctacatttc taggggaaaa 169560
aaaaaaccca caaatacttg gttgtctcct tttctttttt cttttctttc tttcttttt 169620
ttttttttg acaaggtctt actctgttgc ccaggctgga gtgcagtggc ggtatcatgg 169680
ctcagtgcag cctccacctt ccaggctcaa gcgatcctcc cacttcagcc tcccaagtag 169740
ttgggaccat acgcccacca ccatgcctgg ctgatttttt atacttttt ttttgtagag 169800
acgaagtctc actatattgg ctaggctaat ctcaaactac tgggctcaag cagtcctctt 169860
gccttggcct cccaaagtgc tgggattaca agcatgagcc actgcaccca gtggttggcc 169920
actcttaata gcaaccttca cagtataaca atgaactgtc tctrgtttcc tttgtcacct 169980
taaagcggca tggagggagg ggtgttatgc ctcttgagta gataatggaa catcattttc 170040
attaccaaca gggtatggaa atcttagcta gttcaagaat taatctaatc ggtgttagaa 170100
taatgtcttt ctatggtagg gcaatagact caatggctcc ctgctgcttg catctgatgg 170160
caccctcctg tgttgtgact ttggtggtgg gtcacaactc cacatttacc ctatccaccc 170220
tatccactga catgggtggt tttcagctac acatacatgg attgtggtgt atgcatttct 170280
ctcacctgtc tttaccaaca tcwtcttctt tcttttgttt cctattcacc tgcaatgagt 170340
ctggataaaa cccctgttct tttattttgt ggacactaat gatttgatgt cagcatctca 170400
cctctttcct catagcatca tggtttctga caactctgtt agcatatgcc tttcctctcc 170460
accccaatat tgcttggggt ggtagctata atgtagttgg aaaagcacta aatttggagg 170520
agaaagacct aggtttgaag ccccagctct tcacctagtt ctatgacttt gagacatcca 170580
gttaaccatc tttgagcttc agttttctca tctatacaaa tggtgtaaaa atacctatyt 170640
cacattgtgc ttgtgtgatt atactttgta aactaaaaaa agktaccaaa atataaggca 170700
ttcggtatcc agttaacaaa atggtagtgg ttttctgaag ccctaaggga aaaagtatga 170760
ccattctaat gtattttatg gaaaaataaa tgagacattt tattgtattg atttctttga 170820
aaaagccagg gtccaaagca attaaaatgg aatctttgga ggtattttta ttatgatcta 170880
ttattataat agcagtgtaa tttgtctacg tgttttcctc ccatttcctt tcatacttag 170940
aatggtaagt aacattaaag caaagagaat taactgctgc actgagctct catgctttct 171000
gattcttgcg tgctttggtt tcagagaatc aaaactgctc ggattccgag tttctctgtg 171060
taaatgacag acctccggac aggaggtgca ttccccagtc ttgggtctgt gatggcgatg 171120
tggattgtac tgacggctac gatgagaatc agaattgcac caggagaact tgctctgaaa 171180
atgaattcac ctgtggttac ggactgtgta tcccaaagat attcaggtga attgaggatt 171240
cagaagttac ccagcatgcc tcaaatgtcc atgggggctg ggctcactta cctatcaggc 171300
accccgtggc cacagtgccc agggcccatg atgcttttag tggcttatga aaatgtttgg 171360
attcctttcc aaatcaaagg gaaaaaaaac ttttacatca aagaaagtat tttaatatat 171420
aatattaata tatctggctt tataccaata tgattgcatt aaaatgaaaa gaagttactt 171480
gaattattaa tacataatac catattaaca atttaaaatt aaatataatt tttaatattt 171540

ttatggagga aggaacccaa gaaggcaaaa atgcctaggg cctgtgaaag acagaatctg 171600
gccttgcaca gagggccagg gagatgaatg gatagggctt gagataagaa ttctttcttg 171660
aagctggtga cccgcttagt tttccacttg gagtagaggc attggtatta caagaactgt 171720
ttcactctct tctctctact acaagaaaaa taacagcaca agcatgatga taaatagagc 171780
ttggctctta ggctcagagt caagtagagg caggtggagt gaactgagac aatgtctcca 171840
actaaggatg cagacattga tcaatatcat gcagaagggc tggaaggcca gactttctga 171900
tgctctcttt ttgacagaag ttggaaatct ggattttcat ttgaaatact ctgattttaa 171960
atgctggaaa caaattttaa aattcttaaa acactgtgtg gatcaaacag attcggctca 172020
cagcctgctg gtttgggggа cctctcctgc aatgttccat tgtttgactt cttacctctt 172080
tctccaaatg ggcctcttca aacagtttat atacattctt aacatcccaa cttctcatca 172140
tcccacttaa caaatacttg gattatggaa ggaaatggag aagaacaatt tgtaagtttc 172200
aatcctgatt gactaggaaa atagtacgag cattagcaaa agtaggggag tccagaaagg 172260
cgcttgctca aggtggaagg tgagtttgac atagtaggac ttcctgaggt gaaagtatgt 172320
cttaggtatt tgggcacaac tggagccrtg aagagatatt gcttgtgcca aggactgtta 172380
agggacacac acaggcacat tgagagcatc aggaatggcc accttacagc atgcgaagga 172440
agacagtggg aaagatatac taagtaggca caagatcaga gaagcagagt cacaggggcc 172500
attgactgga ggggcaggca gctcatcaac aggcgctaat gtaccrttgg agtccagtgt 172560
ggtgtacgat tgtgtgttta ttgtggtggt cctgaggaag aaggaggagg tgaaggagca 172620
gggactcagc agtaatttaa aaagtagata aatgctatca ggaaaataca ctctgtgggt 172680
gattcatcct ctgatgagtg gacattgctg agaggtgrta gtttgtgaac tgacaatgca 172740
aagacattca agaggtggag ctgtcttctt ttgtagtgaa gctgcagtag aatatgcttt 172800
gtttgtattt aagtaatatg aatgtaaagt gtagattttt atttttgca cctaaagtgg 172860
ataaatcttt gtctatattt tctccctact gctcaagagt tctattgtgt tgcacttcta 172920
tagtttttct gaatttggta aatagctaat agcattagtc ttagatgtaa atatattctg 172980
aatacctagg cttagactct aggcacaaga atggtagcag gtgttgattt tgatcagact 173040
ccaagttatc tcctttattc ctcccattct gagctttctg ggttcttcct ttatcattac 173100
tatgatctca cagcacagta acatttcctc tctccctttc tttgttcgtc cattgttcct 173160
tccttcactt tccctccctt tctctctctc tttctttttt tccttgagct ttctgaattt 173220
ccttgaaaag ggctatagta gaagagaaaa aaaaaatact gtttgtttga aaacctgagc 173280
tatcagcttc taagtaagtc caaaatctgt gtctggagta gcctctacta ggtgtgctgt 173340
tagtgtgcat ctccttgctt gcttggcaga aagtgtgctc cccatttggt acagtgggac 173400
aggagatcat ttttcctatt gaccttcttt ttttcttggc tcactactga tgctgctgaa 173460
aaacatggat gataagactg aggggtgaca atttggtgat gagctggaat actgacttgc 173520
aatagtgtct gaaagcttgg tgatttgctt gatgacttgt ttttcctcct gcattggatc 173580
taaattagac aaaggaaaac attggtgttt tcaaaccatt tggaaatgag ttaaatagct 173640
cccgggagac caaatgaagc tgagccagtc tgccttgacc acagctttct tcacaattac 173700
atgcacacat tttgctgtaa atcatgttga caaggccctg ggtttatgga tggcagtgct 173760
ggttagcagg cctggttata ggtcrgttgt aaaactgacc acattcaccg ttgttgcctt 173820
cacattttgt aatgctctat gtgccgctcc tatgctttct atgataaatt gttcaaaacc 173880
attagctttg ttcactctta tcaaagattc cttgatgcat atgtgagacc ccctttagac 173940
atcataactt ttatgggatc ttggagtaat atggagaaga aaggccagtt tggctcacag 174000
aacttcagga aattatattg ttataatgat gcctgtgtat gttaggtccc gagatagctt 174060
ctagtactac agcatgcctt cttcctttgc cagtatgcca tgctaaccta ctagcttgcc 174120
tttattcaca tcaccatgaa gactcacatc tcatgataga tggcaggagt gtaatgaaag 174180
atggaaggaa caggactgac aatgtaaacg ttattccagt gggaagatat gtgttcttag 174240
aggacacacc caataatctt atttataata tatagcactc accctatgag tttccatttg 174300
ggtatgggca cttttatcat gtgattaccc agtacattgc cagtgcctac tggctatctc 174360
attatctgtt gaacatagat agtgccactg ttcataagct gtctcataga tctgatgtat 174420
accaaaatta caaaagttgt atttaattag tttatcaact aaggaaaaaa tgaatgcaat 174480
tatttttaat agctatagac ctactaatta tctatagcta ttaaatggta gcatttaatg 174540
gtagcatttc taatggtagc agccagcccc tgaggaagtt gtgtggaatg ccaaatattg 174600
gattcttcta gaattggcga ttagtggggt agacgaagat gatgggggaa aggggatcaa 174660
ggacactggt gatcttgtcg aaatggttga cctggcattt aggtagataa agaaggaagc 174720
aaaaccccaa gtgggtaata gttgaggttt attgccaacc tctctgaaag tggtactgga 174780
tctcatgata caggtgtgac cggcacaatg actgtggtga ctatagcgac gagaggggct 174840
gcttatacca gacttgccaa cagaatcagt ttacctgtca gaacgggcgc tgcattagta 174900
aaaccttcgt ctgtgatgag gataatgact gtggagacgg atctgatgag ctgatgcacc 174960
tgtgccacac cccagaaccc acgtgtccac ctcacgagtt caagtgtgac aatgggcgct 175020
gcatcgagat gatgaaactc tgyaaccacc tagatgactg tttggacaac agcgatgaga 175080
aaggctgtgg tgagtacaac agaggatttg ggaaaaggaa acaggggaga ctgaatatgg 175140
attctcaacc cttcacgact tagactttcc aacctgtcct ctaactacaa agttaccata 175200
aaatcactat tcctgatata gcaaaaggtt accaaagttt cttggtatat aagatgggga 175260
cacacatttt tttggaccaa ttctttgctt agatagtcat tagagagaac agaagatggg 175320
caaatattca ggccatcatt taacattatt gccaaataag gtactcaaga atgaagggaa 175380
ccaggttgat tctctttgaa ttcttgtaat gacttttgc ctgaagcatc cctctgctag 175440

aactcgttgg cctgttcttc atttttgtcc tcaggtaatt gaatgggaga gtttaatatc 175500
tctctcaccc caaccaccac aagtaaagca gttgagaatc cacagcatgg gcattgtttg 175560
cttagcacca tcttgaactc cataatattg gcagttcgtc ctgtttgtgg tgtttaatcc 175620
ttgtaaccat tgtttcatgt atgttgatat tgtctctgta ataacaattt agagaccata 175680
tcctttcatt tattttgttt tctttattcc acttgttcat tgtcagtact cattgaaagc 175740
atttgcctaa ttgacccaga agtatgtaat gtagttttta tccttatatg aaagataaga 175800
tttatatgaa ataacattaa aattaaatgc tagacagaaa ctgctgtgga aatgtggaga 175860
agagattatc tatgcataat attaaaaaat ctgtgcagca aaccaccatg gcacgtgttt 175920
acctattata acaaacttgc acatcccgca catgtacccc tgaacttaaa agttgaagaa 175980
aaaaaaagaa aaaaatttaa aaatcatcca aaaactggct tttgctctat tgtaagaaaa 176040
acttctataa atttctacca aagtttcaaa aaccatttaa taaattaaga aaaacatgtg 176100
ctatattata catttataca aaaatcatag ggaactttct tatgtttact cctaattcat 176160
atagattccc attgcatttt aattaatttt gccttacctc aactataaga attaaatcct 176220
caatagtaca taattcaaat taaaattttt agcttgaaga cgaagtgatc tcagtaggtc 176280
tcatccaaac ctatgaaaca ttcactctta caactggaag gagtactagt gatcttctgt 176340
accctgttct ctttgcagat aataagactg tagcccatag atgggaaacg aattgtttgg 176400
gggtgcacag tgaactagtg gaagagcttg gcctgatatt tggataatgg attttgcaat 176460
gcatgaagtt ttaatctatt gctccttgat gagtagagaa ctaataagaa cttgctgtcc 176520
tccctctgta gatcattttt gggtgaggtt gcccatgtgt tacaggacca gccagaggga 176580
catgtagtgt tgtgttgcac ctagtgttga gctcatgcca tctcgtgaga ggcaaatgtg 176640
tgtatctctt tgtggttccr tgttcagtga tgtcacactg gaagcctgag cttgaccatg 176700
gtgtgaacag tcacactgga acatgctaca aatcagagca tttagaaaat ttttcctgag 176760
tcctgtttga ccagcacact ggccaggctc ttttcttctc ctcttctttc tcatttctcc 176820
tgtattagtt gttgaaacca ctgatgaagg agtaagttgg tgaggaagtt gaaaaatagt 176880
gacttttcaa taatccacag tctttggaag tctttgttgt ctgtcttagc mtgattcatt 176940
aagaattggc actgtttagt agaaatgttg actttgaacc attatagtga gttggtcgtt 177000
gatattttag gatctctaag aactgctttt tacctacagg cattaatgaa tgccatgacc 177060
cttcaatcag tggctgcgat cacaactgca cagacacctt aaccagtttc tattgttcct 177120
gtcrtcctgg ttacaagctc atgtctgaca agcggacttg tgttgatatt gatgaatgca 177180
cagagatgcc ttttgtctgt agccagaagt gtgagaatgt aataggctcc tacatctgta 177240
agtgtgcccc aggctacctc cgagaaccag atggaaagac ctgccggcaa aacagtaaca 177300
tcgaacccta tctcattttt agcraccgtt actatttgag aaatttaact atagatggct 177360
atttttactc cctcatcttg gaaggactgg acaatgttgt ggcattagat tttgaccgag 177420
tagagaagag attgtattgg attgatacac agaggcaagt cattgagaga atgtttctga 177480
ataagacaaa caaggagaca atcataaacc acagactacc agctgcagaa agtctggctg 177540
tagactgggt ttccaggtaa gaaaacactg atgagctttt taaaagttaa aaattaaaaa 177600
attctaacca tgttttcatc ttgataggaa attaattttt caacttgggt taatatgcag 177660
atacatttaa tgtttctgca ggtttatttt ctgctttgta tctgatattc aaatgataga 177720
ttcagaacag aatatctaat tattttaaaa atttatagta tcatttttat ggaaagagga 177780
attgcaaggg aagagagttc actgttgctg gccattcact taactggaga tgatatgaag 177840
ggacgattca tgcattcatt ggtgcattca gtcrttactt cctgagtccc tcctacatgc 177900
ccagcgtgat gacaagcagc aggggttttg aggggaacaa ggcagacatg gcccttgctc 177960
tcctgaagta catagscttg cttacaatac ttgtcattgg ccgggggcag tggctcacgc 178020
ctgtaatctc agaactttgg gaggctgagg tgagaggatc gcttgagccc agaagttcaa 178080
gaccagcctg ggcaacatgg cgaaatctgt ctctaaggaa aatgaaaaaa attagccagg 178140
aaaggtggtg ttcgtctgta gtcccagcta ctcaygaggy tgaggtagga ggatccctta 178200
agcccaggag atgcaggttg cagggacyga gaacatgcat ggcactccag cctgagtaac 178260
agagtgagay cctttctcaa aaaaaacaaa acaaacaaaa caaaaaaaac aaccaatact 178320
agtcattccc agcatgggct gggcgtgaaa actggagaat ggctaacatg agactcttgt 178380
tttgagattg cccttatgga aactgacagt ctttaaggca ggccagtgat attttaacta 178440
aactaccaga tgaaccacac ttcttaacat ctctattgaa tatcaaatct atcggattct 178500
tggcagcata aactaattgg ctttgtggtc aatagacatc aatctgcagg cactgtaaag 178560
atgtatgctg taaagattct tgttgcagtc agcccagacc tccagagggc tcttccccac 178620
atccttatat ttgactccct taagggtaaa gatcctaaaa tgggtgggga cagttggctt 178680
cccagttctc cctgaccagt agctggcctg acataggtgc tgagtgcttg ctggataata 178740
aatgaaacrt tgactaagca ttcctattgt atgtatcaat tcctgtttta cgtatcctac 178800
atgtcaaaaa gtatagtgat taatgatttc caggaacaga actgagcatg gtactgttct 178860
tgtcaccatc ctttgttcca ctgcagaaaa aataatattt gaactgtaag acattgtcat 178920
tcagccctct ctctcagaaa ctgctagaat gacgtttctc ttggatttca gctatttcct 178980
ctctatctcg gtgtgttctt tatcagaaga gaattaaata catgtgagga agatgggcaa 179040
gaaagtctgg gtgagggtag ggtaaacttt tcttgaaagt ccaggagggt gcacaaccag 179100
gctcagtgtt cctgaaaaca caaaggcaga atggagccca gttacattta cattggtagg 179160
gggcagttct aagatactag ctacactgaa attagaaaca acttttttct ccaatattaa 179220
taaatatttc tgctgtcagc aytagggtgt ttggtttcca aagcccttgc atttgatata 179280
rctttttaaa ccaccattac gcacattgga agatactgtt ggctctcagt tatcttaatt 179340

tttccagtag tggagacgga atatcttctc catgttttct tgagaagaat ctgttcacag 179400
gatgtctttt gactgtggaa taaagagaaa ttaatgggaa agcagtaagc tcaacagagt 179460
agagtgccct atggggtagc cagtctgcca ggacttgaat ggtaatagca acaggaatac 179520
taatacgaca agaataataa tagcaactcc ttctaagcct gttgtgatct gaaataatat 179580
aatgttttaa aaagtccctg gtctgaggcc tggcatttaa caagtgttca ataattagct 179640
actattattc tcactgttct tagtgtctac catgatggaa tccaagattg tagccatctc 179700
attcatcagg atttactcat ttacccaagt gaattaactg gcaagacttg tacatatatg 179760
gatactcatt ctttcttgct gaagcctgaa gcgatgctac tgtcctaact attcagatat 179820
ccagcatgaa tggttaagcg cgtacttgtt gcaaagaggc attcaggtct tttggaaggg 179880
aaatcattct ccttcattct ccttccggtt ggaattgatt atcaaatcct aaatgacctt 179940
ctcactatag gtgcatttaa ccctttggaa ggttatggat gctataagac tctggtgaaa 180000
gccctgggcc cctttagaaa gtacacagat caccaaagct ggcttccctg attctgggta 180060
aagaccttgg gttaagaaca cttaccttat aagaaaaata aattttattg aataaaaata 180120
catttataac agaaatgtcc ttgaggtagc agtttctaac agatcctaat atgtttctaa 180180
agcttcttag gtttgattaa gtgaaatgtg tctcaggttg agaaactcat tttgacagcc 180240
tgtctgacag aggcagggat gtctctttat cctaaggatg tcataatctt tatcttaaga 180300
atgtcataat tcagagtttc tctgtgcagt ttcaatgaca cacttagaca agtgtgtttc 180360
cttgactcca ccatttaaac tgtaattcat gatactcacc tctgcttccc tgttctgcta 180420
agcctttgca ctgcctggag agggtgcctt atgctgcatg aggaaagtaa aaccagaccc 180480
gtcgaatgaa gtgtgtcccc cgtattttct acatgacacc aycttaaagt gggmattatt 180540
gcacacagtc ttgcaccctc tgttgcctca ctgcaggaag acaaacttcc tgttttcccc 180600
tgccctcatt tgcctgaaga aaggtgactt ctaacaactg tctgtgattc tcaggtagct 180660
tgggtaggaa actgggtggc taaatatgta ccatttcaca aagtgactgt attggttaac 180720
tcctggctct ccattttaga aagctctact ggttggatgc ccgcctggat ggcctctttg 180780
tctctgacct caatggtgga caccgccrca tgctggccca gcactgtgtg gatgccaaca 180840
acaccttctg ctttgataat cccagaggac ttgcccttca ccctcaatat gggtattgtc 180900
tccctgcaat cctgggcttt tctttcacct ccttcttctg cctctgttam cgagaaggct 180960
gttcatgtaa ctatctcaag gccaatgtct tgctggggtt tgtcttctgc ttttcctact 181020
tggtaaattg tttagtgtaa tgagtagaag catggcttct tcaaatcatc atcatcagct 181080
cttctgtttt cttttccctg acacactttt gcacttttca agtcctgtat tttggctgca 181140
tgcaaagaaa actgtggttt cagaaaaccg atttctttac tggactctcg aagtcaaagc 181200
cactgaaatc cagttaacta tgtttatttg tgagcatttt ctgtacattg tccccttcct 181260
ttttcttttt wagattattt gctgttagct ctctttcttt tctgaatgca gaaaagaatt 181320
cagaatgcag tctgctctac agaatgcaga ctccatttct ctaaatggag aaaaggtgtg 181380
tattttggct actgacttct tttggcatca gggactgacc ctttgtgttt gccctgacag 181440
gtacctctac tgggcagact ggggtcaccg cgcatacatt gggagagtag gcatggatgg 181500
aaccaacaag tctgtgataa tctccaccaa gttagagtgg cctaatggca tcaccattga 181560
ttacaccaat gatctactct actgggcaga tgcccacctg ggttacatag agtacgtaca 181620
tagaaaagca taaaacaatt gtgtaactgt ttatttcaaa catcagagct tgtgattcca 181680
gtctattagt cccctctatt gtctaactgg cctgtctgtt ggaagtcatt cgggggaagt 181740
cacacttcta actaaaactg ctgagctcta tggtatggtg cagtagaaag agggtgaact 181800
tttaaatcat atggatcagg gtttatgacc tgatgttttc acttcttatt gtttttttat 181860
ctagaaaatg gggctaataa tctctcccca tggtagtcag ctcagtgtgc aactcatctt 181920
aatttttttt atctctttaa tttgctctcc cctatgaaat atatgattaa taaattttag 181980
tatttgagaa aaggaaaaga ataaaaggat ctggaaaact ttccctaaaa tactttggca 182040
catttatggt taagtgcagt gcagtgtttt aggtggcagt agagtctgtt aacattaatc 182100
caatatgata aggcatttac atctttctgg taataggata attttaagt gtgttaaata 182160
tactgttcaa taaaaaatac tcattgtaaa aagatgatac acattattaa tcaaaaatta 182220
aacaacaata cccatattga attttgctag ttatggccta gttggaccat agtawtgtct 182280
tctgcataag catttatgga taacgatcca ggaacagcct gttgcactca gaagcatgga 182340
aatgccattc attcagtaga actatttcaa attttttttat tttatttttа gaaattcctt 182400
tcttctgtta tatttatttt gctgccaaag tcagtgtagt aaagtttgaa gttctctaac 182460
accatgctcc ctggggacat gccactgaaa aagaaggaat acctggcaca cacgccagtg 182520
ctctttcttc ctgtgctcat ggcaggcata attaatcaat ccaagtactt tctcttgttg 182580
aactggttca tttgctacac taaggtagcc tttagcattc tcattgcaga atttaccgta 182640
gcagatatta actcactctt agggtagaga ctaactttaa ttagaagcag tacaatatta 182700
tttctagttt acttatacca ttttgatgtg atatgctgat ggtaataccc ttagcccttc 182760
ccacagtgtg tgtatcctct cttaaaaggc acatcaaaga gctgagttag ctttccatat 182820
aatcctatat tgaattagta gaagcatcaa gatgttcaaa gaagcttcaa caactttcta 182880
actgacattt gttgttcttt gggtcctata gattattctt ggtcttgaaa gcttagtagg 182940
tgtcactcag catacattta gacagtgttt ccaggagcat tagagatgaa aaaaggaatt 183000
ttctagttac acaatattct gttcactttt tgataaaatc taatatagat tatttacgta 183060
gatggattat aaaatttagg cagtagattt tagtctaaaa gtcaaatcat aatatgaggc 183120
actgtgatct gggaataaag gaaactttaa tattcatgag ccatgttaaa ttggttacct 183180
cttggagagg tagcaatgcc tgtgttcaga aatatatttc atagatgcat aaagcaatag 183240

```
atttttatag agcatgcaat tgattccttg tacatcttgg gatgcaccaa cacatcactg 183300
garctgtgcc tgtagttcta ctcttacttt ttttttgag atggaaattc gctcttgttg 183360
cccaggctga agtgcgatgg cgtgatctcg gctcaccrca acctctgcct cctgggttca 183420
agcaattccc ctgtctcagc ctcctgagga gctggtatta caggcgtgca ccaccacacc 183480
tggctaattt tgtattttta gtagagacag ggtttctcca tgttggtcag gctggtctca 183540
aactcccgac ctcaggtgat ctgcctgcct ctgcctccct aagtgttggg attacaggcg 183600
tgagccactg cacccagctg tgtagttcta ctcttgacaa aaagtactca tagagatatc 183660
tgagatctct ctacagagat tacagatgaa ctggaaggga aggtctcagg actactttct 183720
ggtctatgat ttttttagaa aaacagatgg tggctaggtg cagtggctca cacttatagt 183780
cccagctctt tgggaggctg agcagggcag attgcatgaa ctcaggagtt caagaccagc 183840
ttgggcaaca tgacgaaacc ctgtctctac aaaaattaca aaaattagct ggatgtgctg 183900
gcacctgcct gtcccagcta ctcagaagac tgaggtggga ggatcacttg aacccaggag 183960
gaggaggttg cagtgagcca acattgtgca actgtactcc agcttgggca acagagtcag 184020
actatctcta gwtaaataaa taaataaata aataaataaa taaataaata aatcagatgg 184080
tgactaattt ctggtcattt acctgcatcc ttatcaacaa aggccaagca catcttcaag 184140
ttttcctatg acttttataa gttaccataa attatatttt gggaaatatt tttaacattg 184200
catggctaac attatcaggt ttcttagttg ctagcttgtt ctatctcctg tttgagtttt 184260
aggatctgtt ccaaattttt aaaatattaa attttcacta ttttagaaat gatttctgat 184320
atagacccac agtaatgaaa gcccttggaa ctgagaggac ttgggaattt ggctgtggat 184380
cctttgtaac atcttgaaat cggagaacct tctctggagg tttattcatc tgtaaaagta 184440
ttcgctaatg gtgccatggc acgattaata ataaatgtcc tgctggtgtt tgcaaagtta 184500
accctgcagg cctgtaagtt gtgttcccct caggttatac tgagaatgca actatctcct 184560
agaataacgt cccctcygga atgttaatga gaaggtagaa ttccagtata atattgctat 184620
cttctgattt cttccaatgg tgttggaaga aacaagaatg gtgttcaccc caggatatca 184680
aaagggtgct taatgaggaa catcactata agaggccata aacctacaac agctataaca 184740
gcttcatccg caggaaagca gctgtggtta ggaattagtg attatttaaa ctcctgacac 184800
tattcctatt ttgttaagta ttgctttttc acttctacat cttttgttca atttgaattc 184860
atcctttaag tttaattttt gttttaatta aagactagga gttttgagga tctgaactta 184920
tattatctct aggaggtaga attttattga tttgtgaatt cttttatcct gcaagacatt 184980
agaggagagg aattaccttt atcacataac tgtttctgct tactgctgca ggtactctga 185040
tttggagggc caccatcgac acacggtgta tgatggggca ctgcctcacc ctttcgctat 185100
taccattttt gaagacacta tttattggac agattggaat acaaggacag tggaaaaggg 185160
aaacaaatat gatggatcaa atagacagac actggtgaac acaacacaca gaccatttga 185220
catccatgtg taccatccat ataggcagcc cattggtgag taggtgattg aggggtttgg 185280
caaggttgcc ttgggttatg tgcatgtcat gattgtcttt aagcatgaac ttcgtgattt 185340
acaaaaagtt trttgcactt gttagtgttt tcttcaaagc atatgctgaa agttgacagt 185400
aggcaaatat ctttagagtt tatccccctt cccctgggaa agactaccta gaactcttca 185460
tcttcttaaa actcgctcaa ttcttcaaga tcrtcttttt ttttttcctt tgtttttgat 185520
aagatttaac agttatcatg ttgccatatt tacttcatct atttctatgg gaagactgaa 185580
gtattttaaa ggaattaaaa atatggcatt tcagccctaa atactaaata ctaaataaat 185640
gcatatgata ttgtattgtg tataaattag atattattct tatcttctag aagataatgt 185700
caagagcagt gcgttttagt gttttttaag taagagaact tgtttttatt tgattgtgaa 185760
cttatattcc ttttatgcaa ttaaagcaac tttatgattt agagtctgaa ataaagataa 185820
aggtctgaaa tatattttgg ggatagactg gtttttgtrg gtctgctttg ttgtgatgtc 185880
ttgctaaaac atatgataaa cttggaatta aggaaaaatg agaattagca aaataaagaa 185940
atttagtatt tctttctgga agttaatatt cttcatatca tttttattag aagttcaagc 186000
aaatattcac ctcaaagtgg tgaccaggaa aattagtaaa gatgctgctc agtttattca 186060
tccacattat ttttggccaa acttgttacc tgtatactta gaatgaggga atgaatatag 186120
catctgttgg aaattaaaac tttaacctag gtctaggcaa atgaacataa gctaagttta 186180
ctgcctgctt tcccaggact tggagaaaca catcttttct agtcagaaac accagtgggt 186240
atagctcact tctggtagca tataaatgag ctttcttaaa gcacagggtt gttgcttgta 186300
taactctatc atctgtttta tttaggaact tttgggaaaa tcataaatct aggatagttt 186360
ttttttact aagaggtgat gagtttaaag tcaagatgtg taatcagcta atctgtgctt 186420
gatactctct ttcagcaaat gaacacatat tttcttcctt ttccactagt gagcaatccc 186480
tgtggtacca acaatggtgg ctgttctcat ctctgcctca tcaagccagg aggaaaaggg 186540
ttcacttgcg agtgtccaga tgacttccgc acccttcarc tgagtggcag cacctactgc 186600
atgcccatgt gctccagcac ccagttcctg tgcgctaaca atgaaaagta aggctctctt 186660
tcccctctcc tcagtgcctc tctagcccgt ggacagacat tgaccttcaa ggctccaagg 186720
gatgggagtt ttctagtgag acaagatttt ggttaattaa cttggttcat gtggaacaca 186780
gcaagactct cagcctccaa cttcagataa tattttccat gaatagaagg agcttgctaa 186840
ccaaactgtt atgcctatat atgcaaactt tcatagaaag gaagcaaacc atatatttct 186900
catttctaat tgtcttaagt attggagcca gagtgtatat aagtacatac tgaaaaattg 186960
tccctagaag taatagaatt tcactgtctt ttccatgtct atgccggcct agctccttag 187020
ctgcctatgc taggggatcc agggttacac attcaaatcc atttttgatc atttgtgttt 187080
gctatgaaac atggccacag attatttttct taacaatgtc cacaggccca ttgataacta 187140
```

ggggacctga gttagagagt ggcatggaga gaggcattaa tgcagatcat agcatctaag 187200
atgcagaggt agacgattgt agtgattaaa taagatatct gagattaaga atctagcata 187260
catttatcgt gagaaagacc ctcaacagtt tttattgccc tccaacttcc caaacaatac 187320
ttttatatca ccctggcaga caatctcaac caatcactgc tcctagaaca cagctcaaaa 187380
cacccactct ttatttgttt attgtttttt ttttgtggag gaaatttatt catcatatta 187440
agagcacatt ttcagtttgt atttggatct taagaaacct gttctatctt gccaagttat 187500
gttttctctg aaaatacacc attgtaactg agatttaatt gatcctcttc tagggccacg 187560
agagagctca tgcatgtcat ttcttggaat tcagtgttga cttcttctct ccagataact 187620
gttgcccctg gtgctttgct aaagaagtgc tgtatgttct ctgtgcaggt gcattcctat 187680
ctggtggaaa tgtgatggac agaaagactg ctcagatggc tctgatgaac tggccctttg 187740
cccgcagcgc ttctgccgac tgggacagtt ccagtgcagt gacggcaact gcaccagccc 187800
gcagacttta tgcaatgctc accaaaattg ccctgatggg tctgatgaag accgtcttct 187860
ttgtggtgtg ttgagtcgct ttatgcctct ttttccgact tctatgttga ttgtatacga 187920
tcatgattct gtgggtattt cctgaatatc atgaactaaa aaccagttca aagtcctaga 187980
aggaaactca ggctccatcc tttttctatt tttatgaagt tttttttttt ttttttttag 188040
aaatcttaag gtttttacaa ggcaaatggt tgaagtagac aataagttgt ctctactggt 188100
ggctcttcac catgtgctgg gcattgaatc ccctttgaga gctaacattg aggaggaaac 188160
gagaggtttc caccccccatt tttaacaggg actctcagtt gtcatattta tttatgtttc 188220
catttaaaag gcaaaaaaaa aaaaaaaaga ctgagcacag tggctcatgc ctgtaatccc 188280
aacagtttgg gaggctgagg caggtcgatc gcttgagccc aggagtccaa caccagccta 188340
ggcaacatgg caaaagcctg tctctacaaa aaatacaaaa aattagcctg gcatggtggc 188400
atgtgcctgt aatcccagct acttgggagg ctgcagtaga aaaatagctt gatcctggag 188460
gttgaggctg cagtgagccg agatcgtgcc actgcactca cttggtctca agaaaataaa 188520
taaataatca aataggcaca aaataaaatt cccccaaact aaaaacaaca catcaataac 188580
agtaacaaac acaaagtttg aagactattt tccagtagga gaatagggac agaggaaggt 188640
atgcttaaca kgtcagggtg ttcagttctt atctcttaag tctgtatgca ataaagagat 188700
atttaagaat ttgggagaca gtaatagtca aaagaagaag tgctccrtgt agtagtactg 188760
actgataagt acattaggaa ataagtcctc taaaaagaaa tcatgatcct gctatccagg 188820
attcactgat gtcaattagg agctttcatt cttgatgcct tccaagctga taaccaaatg 188880
tccctgctct cagagaatca ccactgtgac tccaatgaat ggcagtgcgc caacaaacgt 188940
tgcatcccag aatcctggca gtgtgacaca tttaacgact gtgaggataa ctcagatgaa 189000
gacagttccc actgtgccag caggacctgc cggccgggcc agtttcggtg tgctaatggc 189060
cgctgcatcc cgcaggcctg gaagtgtgat gtggataatg attgtggaga ccactcggat 189120
gagcccattg aagaatgcag taagttcctg tgggaggacc aaggcatgac cagagcaggg 189180
agacacgagg aaacttccat ggggactgag agaggacatg gagctttctt tttcagctga 189240
tgggatgctc ccccttggca ctccctgcaa actctggcac tgcaaggcag agtatagctg 189300
tgtggcttgc aggtggaacc agactctgtt tctgaagtgg ctaatacctc cttttgatac 189360
atagaatgtc taaccaacca gaatatgata ccaagaactt atattttata tatctactgc 189420
tttctcactt gagccacaga gaaatgttat gaggtaggga aggtgggtgt gaaccaattc 189480
cattttacag atgaggaaac tgaggttcac attaagtgga tggttacatt actgtttagt 189540
gtcagaccta acacttcaac ccaggttttt tacttcaaac cctgtccttc cccaacccca 189600
cccacaaagt tatactgtaa aacaaatgag tggtgctgac atattgagaa aacttaggac 189660
tatttttctg ctcatggtaa acagatcaca tctaaaacag acacatatcg ccagaggcgg 189720
tttgcttggt aacatggtca ttgttattcc tcagtaccac aacctcaatg tgacaatgga 189780
aaggtgcttt cttgtacytt cagttctgac tttgatgcct cctccctttt cagtgagctc 189840
tgcccatctc tgtgacaact tcacagaatt cagctgcaaa acaaattacc gctgcatccc 189900
aaagtgggcc rtgtgcaatg gtgtagatga ctgcagggac aacagtgatg agcaaggctg 189960
tggtaggagg ggccacaggg gagtggaggg agggacaaga aagtgcacat gtcaagtgcc 190020
atttattaga tgagagatga gagtgtattt cccatgtcat cttttctttg tttacctctg 190080
taaaaaaatg gttgattctt ctaataacat gttacatttt tgtagcattt tgcagggtta 190140
ccaggggtat ttaatttgta gcactttaag tcatgctgtc attgaggaag acgttattaa 190200
gatgttagaa acttgtgtaa tttcttccaa atgtagaatc cttattcata cttgacaagt 190260
ttaaattgtt tctctaattt tataaattgg ttgaaattgg tggaaagggg ttagagaaaa 190320
gacttcgtat ctatctctaa aaaggatatt tccaaattag gatatttctt atttggggat 190380
tttcatattc tgaatgtctc tctgattttc cctgttatct attggacatc tgtagtctct 190440
ctggtaacat gggaaagcca gataaattaa tggaatttgt caagattagt catagtctaa 190500
cttgaaacca aagcatctgg agtatgtgtg ttgggtttag ttggaagaga agtaaggaag 190560
atactaaatt cttttaagaa cactgagtcc aattgactga agataatatg atcaaaatat 190620
ttatttatta tggcatcatt ttagcctccc ataccaggcc tttgttgcaa attacaaacc 190680
agataccatt tcattctttg catggtttct accaatggga atggatcgag tttcaagtgg 190740
taggataggc tcagggtagc taaaagaggg aatgttgacc atgaatgttg ctggcattcc 190800
tctctttggg agcttcaaga gtgagctaat acaattctca gactgtctca caaggaagcc 190860
artactactt tgtgcatttc tctgccaatg gtttatgaag tctttgcaat gactgctttg 190920
cagaggagag gacatgccat cctgtggggg atttccgctg taaaaatcac cactgcatcc 190980
ctcttcgttg gcagtgtgat gggcaaaatg actgtggaga taactcagat gaggaaaact 191040

gtggtgagtg ttcacagtcc tatggtcctt atataccacc agagctgtga tgtttgcttt 191100
ttgtccataa ttcaactgtc tatgtcattg atcctcaatg ggtaggatga tatcaagctg 191160
tctgatctct ttctttctgc tggtcagtac atttctactt tctcttccac taaagacata 191220
agcatctcct tctgagatgt ttcaaatcaa gcttttggag gaaggtattt actgaagaat 191280
atcttttatg tgttgaattt atttacatcc aacttttttt tccaaaagaa gttgaggtga 191340
cttatgataa aggaaaaatg taataagata aatagaatag aaatagaaaa ccaggaccag 191400
agaagtagag ggaggaaggg tgctaaccca gagacactgc ttcttaagct ctttccccaa 191460
aatggccttc ataggagagg agagagaact tgtgtttgca ttattaccct tcctagaata 191520
gttgactatt ttaggagggc taayagttaa ttaacaggac aggttttagt ttctctctcc 191580
cagtcgaagg tattgactac aaggcattgg atagggaggt tgaggaaagg aagccaagag 191640
gctgagatca tatcaaatta gatggtcaga acacactcaa tgtgtgttct gaaaacaagc 191700
ttaatgaagc cctgcccaga gtgtatatca ctgacccatg atatgcgtca atttctaatt 191760
gactaatgaa acacattcta actttgttta ccttttggaa gaaaaaagtg atcaccactt 191820
gcgataagca atgagagatt taggaagctg actacacctg caaatatcag ttagctaaaa 191880
acttatacaa aagggtaatc caattggcat tttgtctttt attaataaaa gtcaatgttg 191940
aatcctataa gaggttatct agagtttcac gaaatagaaa aaattaagat aaaatcaagc 192000
tgggcatggt ggaacacacc tgcagtccca gctacgcagg agcctgagca gggaggatta 192060
ctttagacca ggagttcaaa gtcagcctgg gcaatgttga aagatcctgt ttcaaaaaaa 192120
aaaaaaaaaa aaaaaacaga gagagagagc aagagagaaa gagagatcag atcacctttg 192180
gacaaacttc ttaataaagg ccattcttta cagactcaaa attaaggtga aaggtctagt 192240
tttggagggt gaatgatttg cccaagcaca cctctggggc ttgggacaca ggagggtgct 192300
gggcacccag ggcactatgg tcagctcaca agatgtctcc tgtatgtgat tcctggtgca 192360
cactcatggc caggtgcctt tcctttccag ctccccggga gtgcacagag agcgagtttc 192420
gatgtgtcaa tcagcagtgc attccctcgc gatggatctg tgaccattac aacgactgtg 192480
gggacaactc agatgaacgg gactgtggta actgtcattt gagaagctya ccatagaatt 192540
ttgtactgtg acagtgtagg ggcttcaaat tagtgtttat aaggctttta gaggaaaatt 192600
atttttgtat atgtgtaata tgtaaacctt agcataacac agtatcttyt gctctgtatt 192660
ttctatgcat tattcttaac tcatagcagt ctagattagt cataattgag gaaaatagca 192720
aggaatttta aacatttaat tttaatatca acacttctta ggagcagatt ttaatctgcg 192780
ttagccttgt aaacaaagac attgatcttg ctactattcc acggaaagtc accctaagga 192840
atatgcatgt gctcctatga ctctcttgtg tagagatcag atcattgaca gagtaatcct 192900
aaacccaaag taatttttat agctctttac tgatttggtg ttgggtctta ggaaaattag 192960
aaaacattga arattgggga attccgattt ctgaggaaaa gcttaagagc tggagattat 193020
ttaatattag ggagctaggt acttccatct ctgtatgttg agtggggaaa gtgtgagttt 193080
tgagaatgta ttaatttgct aaccacaagt tgtgggtttg ctgtgagcca gtcacagggt 193140
gtagatagga atgtgatgga gtaaccacta tactccaggt acctaatatc tgtctgaaaa 193200
tgacaaggcc ttctyggaat gacaatcttt tctcttcaga gatgaggacc tgccatcctg 193260
aatattttca gtgtacaagt ggacattgtg tacacagtga actgaaatgc gatggatccg 193320
ctgactgttt ggatgcgtct gatgaagctg attgtcgtaa gtccctagac acatatgtag 193380
tactgcttac ctgagagcat ggatatgata gtttagacat cagtccgctg ccgcttctta 193440
gattaaaagg ccataagtat tgtctgttca gcatgcactg ataatgatca gttcacctga 193500
gttctaagtc atcataatca tacatttcac aatggccgtt caagtgtact tccttgctat 193560
tttaaatgga gaatatatta agtaatctgt gctaacaaag tatttatata ttatcagcta 193620
ctatacaaat cattaattag ataaaaaaca tttcaggtaa aaaaatattc aagcaacgaa 193680
tacattagta taaagaactt gggttgggta ttcgaacata ttgaatttat agcattaaaa 193740
tttttctcag tcacacgatg gagtataaaa atgattaaaa cttgaagggg gccagcccct 193800
ccacacctgt aggtatttct cctcaggtgg gatgagagac tgagaagact gagagagatc 193860
aaaatggagt ttcttatgtc ttccttttct acatagacac agtaactgtc tgatctttct 193920
tttccctaca aaaactggaa agccaacatg attactcaga tttgagtctt tatggatcac 193980
ttgaatcaat gcaaactgtt tatacatcat tattgctgat ccatcaacaa taaccatcat 194040
ccatgataay catccatgat ggttatcgtt gatgatgtgg ttgccaaaga gactttataa 194100
atgtatgtgg gtaaaaccag tcttgacatt tgcctgtaga gattaagtcc agtgctgtcc 194160
atgccatgga tgattcatgc cattggaaac tgactgggct ctgacaactg cccttaagac 194220
atagtccrtt caactttcag acaggtcaag gccactatac atcttgatga ataaagaaga 194280
gcaggctata atggcaagag ccaaaggaga aatagcagga agcttcccca aagtagtcaa 194340
tttgtataat aatttgaata tgtttttttc ccccatggca gccacacgct ttcctgatgg 194400
tgcatactgc caggctacta tgttcgaatg caaaaaccat gtttgtatcc cgccatattg 194460
gaaatgtgat ggcgatgatg actgyggcga tggttcagat gaagaacttc acctgtgctg 194520
taagagggag agaaacggag tgaatgggag tggtgttgtc tgtcaaatct cattgkttct 194580
tacgtgtagc atgtgagcct ggagagcagt tgtacaattg tttaggaatg gacacaggat 194640
cagcgttggt gttatttcac tgggtcttcc agcttcagtt ctctctgtaa cctgagaaag 194700
ttgggaaaac ctccatgttt ttaaatgtat tatggcctta gaaaacaatg tctttaaggg 194760
aaatgttgct tgaaaaccta gtatgcataa ataaaggcag gtctgttgtg gttgaagtct 194820
gaggaagggt agggaggagg ctgtacctct cctgctgtat cctactttgg gtgcccctga 194880
agtaccctct ccaaacccct agagcttcct ggagcacctt tagaaaatgc taagactttc 194940

ttaatcttta cagtcacttc cttttaacat ggtaattcaa ggccatctaa ttccctcttg 195000
ctgaatgatg catatatata tatatatata tatatatata tatattttaa accctgcttg 195060
tttgtgagtc tcaattcagg tacatgtcag tagcagagga ggaggggtat ttcaaaatca 195120
catgccctgg cctcacccta ggcttagacc tgatggagca gaatctccaa gaatgaagcc 195180
tgcacatacg tatttttaaa aggcttctta gccttttagt ttagtcccct ggttgagaac 195240
tactgatttt aatgaagtga acgtaaatag agtttgttgc agtcatwttg ctacatgctt 195300
tgagtcattg gaggaactct agggtaatag ttctcaaaag tgtcttacct ggactaggaa 195360
tgtcagtgcc acttgggaat atgttagaaa tgcaaattca tgggatgcac cctatccaaa 195420
tagaaattaa aaatcaagac caaaagaagt agaggaagga aaggcattaa ctcaaagacc 195480
ctgctttttg agctctttcc ccaaagtggc cttaattttg tgggaaaatt aagggcccag 195540
caatctatac attaacaggc ccctcaaatg attctgatgc aaactaaagt gtcaggattt 195600
tgtgtaagta aaagccctta acctaggaga caagacctgg agaagcactc ctgttggaag 195660
ttcacgttgc atcttccatc ccctttccca gcttcatcac tactcatttt tagcccagag 195720
atttgacttg tgaagatgat atatcttagt attttgtttc tcctcagaaa actttaatta 195780
gtgttcatta tatttcacag ttgcatccca acatttttct ttacttgtta ggaactagcc 195840
ttgttttgct ttgaacttca tgaatcttga gacacatctt agacatgttt aactttcaaa 195900
gaagtcctta ggaaatctct tctctccata aggtaaaatg cccatagcta gtaaaaataa 195960
actttggaga gtcagagaca cagctacatt aaaaggtttc caatactgtt ttataatatt 196020
gaacttgcct ttcacagcaa ataattattg caatagttct attaacaata cttccaagaa 196080
tcagccctta gatctgaccc tttcccctca accaatctta ttataagtct ctcctcttga 196140
tccctgtgtg tgataccaag gcggaaggaa aatcagacag cccaaatcct ccatgtgaaa 196200
gacagaccac atgtgaagac cacatgtatg ttgagttcac tgcatttgtg gtacacgcat 196260
agtgaaccat gttccctgta ccaaacaagt aggggacctg gggactaccc ttgagttcct 196320
cacatctgta caggcagcag ctagaggtct cactctggac agcaagtgtg tcagggtttg 196380
attgtgagat atcgatttta aatgtaagag gtgagggaat tcaggaagga aaatccaaca 196440
caatttaaag cttcaataaa agactcatgc ggtagagact ctatgacaac tgccatcagg 196500
aggatcaaac aaatggcttc ctggctgtta ggataagagt ccatgtactg ccagtctgtc 196560
cagcctcaca gccaccattg tgctccacga tccatgctcc agccaccgag gcctttattc 196620
aggtccagag acctgccatc ctcctctctg actcagaatc tatgggaagt ttcttccaag 196680
ccttcctctc cctaacttaa gtcagatcac cccagtagat gtttcatagt tgtaattgaa 196740
tggttaattt gaaaagcctg tttctctact agaatgaaag ttccatgagg acaaggactg 196800
tgtctttctt gtttcccatc atatctactg cctagcacag tgccttggtg tgtactatac 196860
atgtaaggtg tatctgctga ttgattaatc aaatgagtaa atgagtgcat gaatgaagca 196920
agcctggtgc tgacactgga gtattttaga tattgacact tagattctac tgttaacttg 196980
taatttcatt tttctatctt tcctttcagt ggatgttccc tgtaattcac caaaccgttt 197040
ccggtgtgac aacaatcgct gcatttatag tcatgaggtg tgcaatggtg tggatgactg 197100
tggagatgga actgatgaga cagaggagca ctgtaagcaa aagtcaaaag ggagaaggaa 197160
aaaggaagga ccccaagtgg tctgcagttt ggaaaatgtg cctctgggat ttcagtttgt 197220
tctatagagt tgtgcccatg actgcagatc tctgctgaca taattgttta caagrccatg 197280
caaacacatg cattgcttac atgtaaccct gcctgtttct tcctgtctca tttgagcatg 197340
atgctggcaa atccattaat ttttcagtct ttgtttgaac atttaataag ccttcccctc 197400
ctcttttctc ataagaaact gagaacaaac actaaatact gattgagcca cacctcgcaa 197460
attaatagtt tatttttca aatatgagat ttgatcatcc ttcagccttc aggagttgct 197520
aattgctaat ctaggcaggt gcccagctgc agagatcatg tgaagcaagg cagcactggt 197580
gttaacagag cttatctaat atccttgttg aaaatgaaag ttcatttccc agaagagaaa 197640
agtgatagat tagtttaaga tagaagttcc aaactggctg catttaacaa tcgaggcatt 197700
gaaatagctg tacttttttct gcactttcaa aatgttttaa aatctatcca ttgaagggga 197760
aagttgacca attttctggg caatttaatt tgcctagaaa atgtcagtga ggaaaatcat 197820
ttccccgact ccaattattt ttttccccaa aaagacatta tctgggaaaa ttaagataaa 197880
tgcctgattt ctccactttc tatttcttgt attgatgtgg tcttagaacg ctttgccaca 197940
gaatgcttac ttccagcccc catcccagag gagactgtca gggaggactt tgacactacc 198000
acaaccttca agttcgtatt cctgttatca ttattactgg cagagatagc attaatacat 198060
tatagcatta atatgtttat ttgaggcata gcgcaaaagc atgaaagccc agaaataaaa 198120
tatttttaaa gaatttgagc agatttcccc cttccccaaa atctctttcc atttcccctg 198180
ctaaaaatgc catttttttaa aaaatggagc aagacatttg tagcacatgg tcaaatccca 198240
gagtggaaaa aagaatccat aaacttctat tcttttcaag gaacagggtt ttagtctggg 198300
agaccactac cagtcaccac aggaagcaac ctgcaacatt tcaatggctt aaaatggcaa 198360
aggttcattt cttgctcatg taaagtttaa tgacagtcaa gcaaccctcc tccatcccat 198420
aattatgcca tcagggacac attcaaggtt gccaaggcag gagaagatca acatggtgga 198480
ggcacacagc ttcttaactt cctgagcctg gaaatgacag acatcctctt gctcatagtc 198540
cattggtcag aaccagtcac gtggccctgc tctaactgta agggagactg gaaaatgcaa 198600
gaatatgcat tctcatacaa tttacccttg tgtcactaaa tactccttta tgattttctt 198660
ctcacacaca gaacaccctt aaccccttcc caagggacat agctcatagt ccattcmgaa 198720
actgaaatcc aggacctctg ggtaatgggc agtagccact caatcagttc cagatgtggt 198780
tcctcttggt tgrgagaccc ataaactaat aaacaatcag tgccttctgy gcctgatagg 198840

tattggcgga acaggggcaa cacaatagaa ataaacactc ccattggaaa gaaagaattg 198900
gagactcatg gccatcacca atgtatagca attctgaagt cccactgggc tgggatgaca 198960
catgttagca caggacagtc ctgattcatg tctgctgccc cagtggaatt atgaatagca 199020
ccaccttcac tttcaaaagc acactggctt ggaaaggaga gtaaattaca tggccactct 199080
gggcagacat tgtaaaggtc ccttctttgg ggagtggagg gtatttattg attagctcat 199140
gcctctgctc tgggaggagc tcctgtgtta aaatgtctct cactgtttct gactctaccc 199200
tttgagagtt ttttcttgtc tattttcctc tgcaaatgaa gagggaaagg gaaatatgct 199260
accattaggg ccagcacggc agctttctca ccccacttct tgcttataga aggtcgggag 199320
cccaggagtt gttttttgtt tttttttcca agtctcaaac agtcatagta ttttggttta 199380
tttggttata tctttctctc agaaacatac caggcatttg atctgtttgc ttctagcctg 199440
ttctaaaagt tagtaacctg acctagtgct cttttggaga catagttctc aaatctgctt 199500
ttttctttgc tttctttcct tcatagagtt ctgtctgaac ttattgtcac ttacatccaa 199560
tccatgtaga aaaatagatg ggcagtcatt ttatccaatg aggaggtttt attgggcctt 199620
cgtgtctcac agccttttaa acttcagact tttactgttt gggatgtaga tacaggtggc 199680
ttttctcaca cagcaaattt ctgggcttta ttttatttct gcttgtaagg taaccagttc 199740
ttcccttagg ttctctcttt cttatactat cttgccaaac tcaggaatgg caatcaatgc 199800
acattactaa cattctatct tctaacctcg ctccatgatt gacaggttca gtaagcatgt 199860
gatctgcctt ccagtttttc cgaggtgata gctttatcaa atgctttgac tttgcataac 199920
atgatctcca cctttcctgc ctccactatc agtgtccttg ttgcttgcct cctgactgtt 199980
aatccaatgc caaatatttt atgtttttat tatggcagta ctctacttcc ctcatcactc 200040
tatgttattc ggagtaatta atactagctg ttgcaaccag catatcctga aatctcaggg 200100
gtgtaacata atgaagcctt attgagcact cataaaggcc aacgctggtt tcacagccct 200160
cctgcatctt gcagctgtgc tgcctggaac acatggcttc caaggttgct gcagcagcac 200220
aggagacacg gaggaggcac gtgtgctttt cattgcttca gcccagtagt gacacrtggc 200280
acctccaact gacagtacgt tggctagaac tggtcacatg gtcctaaccc agctgcaagg 200340
gagactggga aatgtaggga agcactygtt tatttggtaa gcacaaactg tctctgtcaa 200400
agaaggaagt atcttgcttc ataaaagaaa aagttttgat tttaacttgt ttttacatkg 200460
caggtagaaa accgacccct aaaccttgta cagaatatga atataagtgt ggcaatgggc 200520
attgcattcc acatgacaat gtgtgtgatg atgccgatga ctgtggtgac tggtccgatg 200580
aactgggttg cagtaagtaa acacttgttt ttatagttca ttgtagtaac tcaggtttac 200640
ctaattaaaa catgcaataa cataatgtag acactgacca cattttctcc ttaatgtact 200700
ttttgcttga attccagtca agcccatagc tagctgtgac tgagtgctta tcctagacca 200760
gacattgtgt caaacattct acatgcctgg tagcaatctt atgagttaga tgttattatc 200820
tctttcttat gtacaaatga gcaacgaact tagaggttaa acgaattggc caggtcttac 200880
tgtcattaag aggttgactc aggatttgaa ctctggtctg tttcactgca gagcamgtcc 200940
tcttcccagt ccactgggtg cctcttagca ctttaaggct acatattttg tttattagtc 201000
tgcacattat ggtgggagga tgggggaggg atagcattag gagaaatacc taatgtaaat 201060
gatgagttaa tgggtgcagc aagccaacat ggcacatgca tacatatgta acaaacctgc 201120
acgttgtgca catgtaccct ggaacttaaa gtatatacat gaaaaaaatc ttaagccaaa 201180
tgcagtatcc ttggtacctg aaaatccttc tgagggtgtt tgatcaagaa gggaacgcca 201240
caggggacct gggaagggac atttattttt atttttaaag ttgagggagt ggctggatgc 201300
agtggctcat gcctgtaatc ccaacacttt gggaggccga ggcagacaaa tctcttgagc 201360
ccaggagttc aggaacagcc tgggcagcat ggcgaaactc cgtcttaaca aaatacacaa 201420
aaatttgctg ggtgtagtgg tgtgcacctc tagtcccaga tactcgagag gatgaggtgg 201480
aaggatggct tgagtgcagg taggggctgc agtgagctgt gattgtgcca ctgtactcca 201540
gcctgggcaa taaagcaaga ccttgtctca aaacaaacaa acaaacaaac aatcaaacaa 201600
aaaagaaagt agagggagca ctttgtgtag gaaaaggatg atgaacataa ccaaggaaca 201660
attctagctc aatattttga tggaaatgtt aaaatgacat gttactaagt tacacctttg 201720
tagtccattt atgactcata aagtgctttc acatacatta tttaatgtgt tactcaagtt 201780
agccccrttg agttgctktt attgtctatg taataaagct cagagagctt aagtaacttc 201840
cttgtggtca cacagaatgt cagaggcaga attggagcag tcatgtaagt ccaggttagg 201900
agggctggcc tctggatccc tgccactagc tgtgccactt tgggcacata ctgacctctc 201960
cagtctttgg tttcctcaca ggaaaaagga ggcccttctc caaactctag gagcctgtga 202020
cttagtcatc ctagtgagct ccatgtgctt tcaacttctt gggctctaat tgacttttтc 202080
ctgaggcatc caaaggattt tctatcaatt tttctcctgc gtgagttacg aagaggtatg 202140
aataaccagc catattgagt tggcttgcca tttatttcac atacgttttc tgtgggactt 202200
ggagttattg acagaatgaa gtgacttgat aaaatatttt aaaagcctga acatgataga 202260
atttgcaaaa ctgaatggca ggtttgggtt ctgactccca gagactgata ggtggcttaa 202320
aatagactac agtactttct tttcaaatgg catttaatta gtagcaggtt tttgtttttt 202380
tttttaagga aataagtagc acaaacaatt cgggtatgga agcagcttct cttttcagat 202440
attaagtgaa tatgtgatat ggaattcagt cttatttctc tgggctaata atttgaggca 202500
tagaattctt ttttaatata ctagttcttg ggtgctgtta atttatttgc ctttgtcttt 202560
tttctccttc ctcctcttct ccttcttctt cttccttctc ctcctcctcc ttcatcttct 202620
tcttctccaa aagcatcact gaagtgttta agacacattg ttcgattttt taaaattgaa 202680
ggtatacaac atgacatttt gatrtactta tatatagtga tgtgttataa tcaagcaaat 202740

taacatatcc gttatctcac atagttatct ttaaaaaaat tatttttgtg gtaagagcac 202800
ctaaagtcta ctgtcttggc aaattttygg gaatgaaaat acattagcat tttttctagc 202860
accattcagg tataaaggaa agaaattaac ctcaggttgc aaatattatt tatgtgatca 202920
taaagataga ttgacttgct gtttctctgg tagttcttat tccttcttca taaaatggaa 202980
agtagggtat ttcttttata aatagagtgc catatgtttg ggtttgggga aatcagttat 203040
acgggttaaa atggtgatca ttttcaaatg aaaacaatga taagaaagcc ctcacatttt 203100
aggaagaatc ctacagtgtc gtgtggtttc tgctcttgtt aaggactctt gcttcacaaa 203160
agggtgactc atttagtgga tcacttggtc cagaaattct tgactcctgg gacccctaat 203220
ccctttatag atttcagagc taggaggaaa ttacaaagtc tagtgatgca tgtgagaccc 203280
atggaggtta tgtgactggc tcaatgatat ccaagttaat aaacataggt cagattcatt 203340
tagcaatgta gaggggatat cactgctaat ctcacagaaa ttcaaaggac agtaaggaaa 203400
tactatgaca aattttatgg caataaatca aacaacttac gtgaagtgaa taaattctta 203460
gaaagacaca aaactctgaa aatggctcat gaaaaaaata gaaaatctaa atagatgttt 203520
taacaatgta cagttgttaa gagctcctat aataaaggct aggatcttta ttataagact 203580
ttcatgcata cagctttgaa gtctgcactc caagggcagc attccattga atttcattgt 203640
actttatttt ggttattttt ctttttgaaa cccagtgttc ttaatgtact cagaccacat 203700
atagtgatat gatcatttac cctaaaggac tctgagagtg attaagttca cctcattgca 203760
tactatggaa aacagataga tataaatcta ttttgatttg aaagaattaa atcaggagat 203820
accacagtct ctttggctaa aatactcaga agcctatgac caggagactt tttatttgag 203880
aggtagatga agcttaaatc cttaatggag ataaccactg cctctctttc ccccattatc 203940
actcactatc tatgttcatc ttcgccagtt tttctgtaag acctaggttt ggggatagat 204000
ggaggataaa agaagcaaac tgataagaat gacaaggatg aaagccagat ggcttggata 204060
gatattggta gagacaagat cttggggcaa tgatgaacaa tgaagtgtta gggtaaagtg 204120
tgagctgtta aaagtctgtc ttggaacatc tggatcagaa taacagggat catttatatg 204180
ggctctacaa aaataaactg tgtttttttt ttttttttta ctgtgaaagt tcaataaaaa 204240
tcaaaagtaa aaatcatttg aatcccatca ctaaaagaga actaaccttt aaagtttggt 204300
gtacttttgc tatctttttt ttgcatatgt atatgtaaga aatatttctt agtattttga 204360
aaaattaaga aatattctat actaaatgga gtttttcagt cttttttttca atttattata 204420
ggtatttccc atgtcaaagt atcatttgaa actataaatt ttaataatca catagcaatt 204480
catcatgtag ataatcataa cttattgctt ctaagatgta ttttttttata ttttaacatc 204540
tttgaaacca agatatatat cttacaatta ataacatgtc agcgtaagtt ccagacatat 204600
tcaattttag tgttacataa agtaatggtg catcattaat gtcttagttt ttttatacta 204660
taacataatt tattccctat cactgaacat acattcaagt tgtttacaaa tgttcttatt 204720
gtaaatattt ttataatcct taaacgtaaa ttatactgca tattccttct caagggaaaa 204780
ttcattaaca tggaataact gggtaaaaga gtatgaatat ttttaaagtc cttggtgcat 204840
acatacatag tacaaaattt ctttccttgt gtactaattt atggctctaa gagcagttgt 204900
atgatttaga actctatgta ttttactgca mcctggtcaa cacttgatat acatgtatat 204960
atttgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtatataatc aattggtcaa 205020
tgttagggaa attatagtct tcttaaaatt ttataatttc ctcctatttg taactttgtt 205080
ctaacctatc tgtatccatg tcttttattw atttatttat ttatttattt atttatttat 205140
ttatttattt ctatctgtta tctatctatc gatctatcat ctatctctct atctatctat 205200
tgatctatct atttgcaata ggattaaaga tagtagagca ggtggtaata gctgtagagt 205260
gtcaggcttc atagttgtgc agtccagaat tggatgctct gaggataagc ctaggagtgc 205320
tgcatataat gtgaaaattg cctcamagtt ttagcattat atgcatttat ctaaatggta 205380
ttcagatcac gatcagaaat aggaatcctg actcccccag tgccctctgt cctctccaag 205440
gcttatggaa aggggttatc tcaagatgtc ctatagttgg ttacgagtag gtgcttcttt 205500
tgatacacca cttgactgtt atttgtggct gatctggttt gtaatgctgg gattttgttt 205560
ttcagataaa ggaaaagaaa gaacatgtgc tgaaaatata tgcgagcaaa attgtaccca 205620
attaaatgaa ggaggatyta tctgctcctg tacagctggg ttcgaaacca atgtttttga 205680
cagaacctcc tgtctaggta gagtatattt tttccaattc ctgtttaggt gaactttaca 205740
tctaaggttc tccacccact ccccttttgtt aaataaatca ctatttaatt cccttaatgg 205800
taccatactc atggtttcat ggttctaggt cattaaacta ctcaagaatt gctttccccc 205860
acctgcatgc atgctatctg accagtgcct acctgagtgc ttgtcagata ctgtgtgctc 205920
agtagagtct gtggaattga tatgaatgat gaaggccttg gtgatgatgg ctgcttattg 205980
caccagtgtg tgaaatcaaa gttaatttaa aaaacaaact aggcttactt tcttcattgt 206040
aagtcaaaca accaacacgt atttattata cacctactta cgccagacat agatgagttg 206100
taaggtatgg agtcagaagg tagcttatca agatggtgag tgatgagcat gattttaggt 206160
gccttttagt atttgaattt actgtttcta attcatgata tgtcatagtc agaagattgt 206220
aagagttcct tttggacttg aagcttaaga actcaattga aaaactaaat caatgactcc 206280
tgttcctgaa gctggttagc agaagtgaag agacaccgaa caatacaaca caacatatgc 206340
cttctgaaag ggaaaatgtg ctctgctatt gcagagtcat agagtttaaa tcctgtctcc 206400
attgcttatc agctttggga ctgtgggctt aatcgtccat acctcttaaa gtcttttggc 206460
aagactaaac gaggaaaata tttgaaaagc atgtgaaaca gtatctgaaa cttagtgttt 206520
cacaaatgtt tgtatcattg cttattttca tctgtaccct tctcggtcct cattgctggt 206580
gaatatgggt ttaaacagaa gcaagatctc taaggaatgg atgggaacag atgttgcgta 206640

tttggtttta ttttgcctac agatatcaat gaatgtgaac aatttgggac ttgtccccag 206700
cactgcagaa ataccaaagg aagttatgag tgtgtctgtg ctgatggctt cacgtctatg 206760
agtgaccgcc ctggaaaacg atgtgcagct gagggtatga tgggttcatg ttgggattaa 206820
ttgacttttg gggaaataaa tactgctaag tacactatac gatgaaagaa acttcagctt 206880
ctcatagttt ttcttttctt tctttttttt taaactcgcc agctgcttct cttccaacac 206940
ctctttagtc gctccttctc tctcctcccc tgccagctta aaacaatagc tacatccccc 207000
aacaaatatg tagcaattaa aacaagagcc aggtgttact tattataatg gatttagcct 207060
cttgtctacc ttgataaaaa cttcaaaaag tggacaagat gtcatctttc ttaaggctca 207120
aacaayaaca aaagcttgcc tatgggatgg tcatcaataa aaggaaggta acaaggccct 207180
ctagctccca ctccactgag aataagattt gaggcccagt agtccaagag ggctcgtgaa 207240
ttggggcaaa tcaaggacat atccctttg tattgttcat ggactactga tcacaggcag 207300
aaaggagtct ggcacagtca taacttcaat catgagtttt acgttttagg ttgatgccag 207360
tgtctgacaa tcgggcctaa taaaacagag aaagaatgta agtcagatgt attatactcc 207420
aaattccaga ggcctgatct aaatcatcat atcctagtta agaggcatgg gtctttattt 207480
tgaatttgaa gtttgtacta gagtttaagg aacttgataa gaaaatagca ctttattttg 207540
taaattaaga gtaaatggcc aaaatggctg ttcaatttct tcatacaaat tgagctttta 207600
aagcatacat ttgactagca tacttacata ttttaccctc aaaacactgt tgacagtgaa 207660
tgaaaactag agtgaaagca tttgaacagt tggtctggta attaagcagc aatttttaa 207720
atgtttaaat cctttaacta aggacatgac tgaaacaaat tggaatattc atataaaaca 207780
taatgtcaag atagaggaaa tatataaaat gaacttttaa aagttactta aattggattc 207840
agttgacatt atgcaagtaa attaaactta acaaattcta gacagtgcat cttgggatga 207900
gtcaccatta agtagctgct ttaggttaaa aaaattaaat caaggacaag ctaggtttat 207960
tttgtcatta gctaggagct aaattgggtc atagagctga ttacctgcta aaaagaatca 208020
taaaatctgt caggaaacag taaggaatga gacttttctg gtaaactttt agtaagacta 208080
taaaagtatt tcttctgtga gatagaatgt ctgcagtctw gtctgttttg atgtcagtaa 208140
ataaaaacaa ttcagtgaaa atgaggactg tacgtagggt tctcagtcta gctttgttcc 208200
atactaccac tgagtacaaa gaataaagaa ctgataatgt ccctaagaga catattagct 208260
ttccacttga agtggagaat gtcaagtcac ggattttgta acccagttgg agagtcagct 208320
ttattgatta acagagatag tcagattcct ataaaaactc atgttcttta aaaaggggac 208380
aggtacatac tgtgcatttt atatcctact ttatatagga aagtataatt caaacagata 208440
aagtagccct ttgtttgttt acaggtagct ctcctttgtt gctactgcct gacaatgtcc 208500
gaattcgaaa atataatctc tcatctgaga ggttctcaga gtatcttcaa gatgaggaat 208560
atatccaagc tgttgattat gattgggatc ccraggacat aggcctcagt gagtataaac 208620
tttggcatct ttcattgata ttaagtgact ttatagaatt ttaaggtgtt gacttttaag 208680
gaatttattg tttaatgagt gaattttgtt gcattagtgg aggaggaaac tcttccaatc 208740
cagcatgctc ctgatgcctt agcgtggcct tgaatcccag ccaagctttc ctgatttctt 208800
tctaaaactc ctccgatcac tggggtttat cctttctgga ccatctcaca tcttcttgta 208860
ttttgaaatt tccttgtcct tgatactgca gatcttgttc cttcctacca ttgtacacct 208920
tgaaaatttc tactcagacc tcaaagaccc agtttaatgt caccacctct gtgacaactt 208980
ctatcactcc ttctggcaga gttctwtgat tgctcaccat gaatctatgt cattttatgg 209040
cacatgttac tctaagttat atagctagtt gaccacataa tatctttcta tcctctagac 209100
atctgctttt tggggacaaa gactgaatct aatttatctc taaatgccta gcagctgacc 209160
caacatctag tacactctat gtggtaggtg atcaaaaaat ttagttgaat gaaggaaaaa 209220
gatgaataat gcttattgtt gaatctctca tggctctatc tggtgttggg ggagatgaca 209280
gtagggtagg agtcagaaaa cttgtcttct gtgcctgtaa acttatcttt tatgccagtc 209340
tcccttatct actagctttg tgatcctaaa taattgtaac gattctctga atctcaattt 209400
tttttctaca aaatcaaagt agtaatcttg ttctgtctgc ttacctctga gagttgtttg 209460
gaagattgaa tgagatagta gatatgaaag gctttgaaaa ctatcaataa ctataccaat 209520
gtaggattta ttattggtgt attttcacac atattcatgc aatacaatac acttttcaag 209580
aatggtgcat acctaggaaa gcagcaggtg tccagtgcat ccctctacag tcacagtctt 209640
cctatgcttt taacatgcct gctgtccacc atccttctgt ctgtatataa aataggactt 209700
ctcgttgaca tggcttcttt attgcctctg atcttgagta tgctttcaaa ttctcaacag 209760
cctgccctgg tttatctcta tacattctgt tttggaaact agaacttgat cctaataaga 209820
gtaaataagc actttgttga aatacgttta aatgaatcac ttttaaatag agatgactaa 209880
atctcactaa gttctcagtt gaagcatttg tagctcatag ctcaagtttg ataggtttta 209940
aagtttgatt atactgatgt cattgaatta ttcatattat aacaacagtg aggagggagg 210000
tagagatgtc aataaacgaa cagtacttca cctgattaga cccctgttct tcctttactt 210060
gatgctcttg acatgaaact gacctgtgtg tcttcctctg taggtgttgt gtattacact 210120
gtgcgagggg agggctctag gtttggtgct atcaaacgtg cctacatccc caactttgaa 210180
tccggccgca ataatcttgt gcaggaagtt gacctgaaac tgaaataygt aatgcagcca 210240
gatggaatag cagtggactg ggttggaagg taaatttgcc atacattccc cccttacctg 210300
ttctgttttc ctggttagag ttctctactg cactccatgg gccatgagtg agtctgggcc 210360
tggatatgag tacactcagc catgggtgca gctgggcagt ggttgggctt gctgaagccc 210420
cagcaactac ctccacttac cccagcatgt catggagaca ttatcatatc ctgtattctt 210480
tgtgggccat gaaaaaaatt gggaaagcac ccaggtcaat atctggatat agatattata 210540

tctaggatat aatagtgaat attatattta ctataagtga atagcattct tgccaacaga 210600
gttctggatt ccaaaagtaa ctttcagtat ggcagcactg ctcattttgt gaagaaatgg 210660
gacagcctca caattctccc agcaaagcag ttgagatgaa actttttttc tatggtagtt 210720
atcttgggga cgaacaatcc acatcttgtg tttttagcag gcttctagtt aaaacagatt 210780
ggaaatttga ctaaagaagt ctttggaatt gagttaatag aggtgtcagt ctcttctgtt 210840
cttctagacc ttctagtggc ccagggacca gagccacaca ttttggatgg tttttaagta 210900
gaacttaagt agggttatca tcaggtaggt gtgcgaggta caaatggatg tggagaagtt 210960
agtaagctca ttcttcaagg aagaggtttg cactgactta cattggtggg aaaatgattc 211020
cttgaaaatg aaccaataat gcaaacatgt ttgaggggga aggttcagga gwcactactc 211080
tcctggagaa tggatagtta ttttcagtgt aaattctttt tcaccttta aaaaatgtgg 211140
ctggtgttcc tggaagagca tctttgaaga agctaattgg gtcccgctgt gyctgcaggc 211200
taacaggaga ctcattttag cattttcagt caagaaacag ggccttagag tactgttgct 211260
agagtcagga actcaaaact ccagacatta acactctctt ctgaaaacca accagggaat 211320
ggcagatctg tcttcttgtt tgaagtttta cctctktctc agccttaatg aataagagaa 211380
ttaagaaagt ggtggaactt tttctgcttg taagagactg agacctgcag cctcagaagt 211440
ggaaataagg caggacagtc ttgccgagtt tgttatttta aaaggctgtt tccactcatc 211500
tttgagctga caccaggttc ctattgattc taacggggct ctttcctgag gaggaaacag 211560
actcatgggc agtcagagtt aaggcaccag ccccaccgtg ccttatgact tctacctaga 211620
agcccatgtc tcataataat gccagtcaga ggccagtctg actgctgtgt ctatggtagt 211680
tatcttgggg acgagcaatc cacatcttgt gtatttagca ggcttgtagt taaaacagat 211740
tggaaatttg actttcctgt ttagtctttg gaattgagtt aattccattg tggatcctgc 211800
gtgattcagg tgctttggct gttgggcagg agtcccctca attccttact cttccaagtg 211860
taacctgcca aacatgtccc cttggctgta gttcycccaa gagaggggga ctatggtctg 211920
atgatagkta tctgagcagc tgtctcacca gccaaacgaa atgctctcat cttcaaacct 211980
cttacccagt aatgattact ctaggctttg cagttgttta actttgtccc tctgaattca 212040
ggcatattta ctggtcagat gtcaagaata aacgcattga ggtggctaaa cttgatggaa 212100
ggtacagaaa gtggctgatt tccactgacc tggaccaacc agctgctatt gctgtgaatc 212160
ccaaactagg gtaagtactt ggagaagtct tcaacatcta gatatttctc cctggattct 212220
catcaaattc catgtttctt ataatttttt tttcctagtt taactgaaat tgtccttcaa 212280
gtttttggga gtagcgtcta tgactgtttc aagaattata acatgccctt gagatcatat 212340
agaaccaacc atttctgatg gggaaattcc tttagaacac atctgagaat ctttctagtt 212400
acatggattc cttgccaaat cagagctctg aactctaaag ttctttgtgg atataactgt 212460
tttaagtgaa ggtttcaaca gaattgtttt tcctttcatt tggatgtttt aaagtaactc 212520
attcattgaa atccagctag ggatttggtc atatttcatt taaaaattaa acatttatat 212580
ccaaaatata taaatattta aaatgacaca tgtataaata tatattatcc atttgtakaa 212640
atattccaat ttgcaattta tctataaatc atctcagtgt aaatgagaac aagttttgtt 212700
atttttctct acatttcaag acatttattt gaataatcac taagctgaaa tgacttggta 212760
tttacatatt agcttagctt cagaatagtg acactttaaa aaagtttttt gaatgacccc 212820
aaataatttt cctacttggg caggaccagt ctagccctct gtagatatgc cagtatttgt 212880
aggtagaacc ctatgagctg ttattacttt aattctgtta tatttcatat gttaaatcat 212940
accctcagaa actcagcaat gaaatatgaa aaatacttga ctgatgagat taacctgtag 213000
tgaggacttg tcctcagcat tagtcattgc tgcttatatc ttatctacac aatatattag 213060
gagcaaagag atgcagtgtg ttctatggtg tgaatgatgt gactgtttcc agtgtgccgt 213120
ttaatttttt cctctgtaac taatgtttaa attcatctga tattattatc atactctgat 213180
atccctccac tgttttttc atagaaattc ttttttttt ttaatttttt tggagatgga 213240
gtgttgctct gttkcccagg ctggagtgca gtggcatgat ctcrgctcac tgcaacctct 213300
gtctccaaga ttcaagtgat tctcctgcct cagcctcctg gcagctggga ttataggcac 213360
ccaccaccac actgggctaa tttttgtatt ttcagtagag acagggtttc accatgttgg 213420
gcagcctggt cttgaactcc tgacctcagg tgatccatct gcctcgccct cccagtgtgc 213480
cgggattaca ggtgtgagcc accacacctg gccagaaatt cttattttag tctttgtaat 213540
tcctttctct ctggaatggc tcagtgtagt cctgtgaggg ataggaagta agaaaggagt 213600
gagaaagggt ttcactgcct aaggcctgca gacccgacct acaacctcct catttcatga 213660
tccatttgaa aggctcatca tccataagtt ttataagcat aagcatatat gatgtgttga 213720
accttcttac agcttctgcg gtataagatc tgccagtggg tccaaaggat gatgaagatg 213780
ataactactg ataataccag caacagcaat gagaagtgcc aacatttatt ctattcttgc 213840
tgtgtgccag ctactctgct aagtgtccta catatataaa ctcatttgaa ttgtacaaag 213900
gatctataaa ttagtcatag gtttctatcc cttatttaca tagatgggta aaataacacc 213960
atgctccttc agacagcaac tgttgactat aatataagat acaaagggag aattgtcatg 214020
aggacactgc tgaaaaacac tgtgatagtt ctcctacctt acaagggttc agggaagctc 214080
tatggaraaa gtakcactga actgaatgtt gaaggttggg atccactggt agtataacca 214140
gtgataaagt atgtgacatg tgaggtcaat gtgggtgaga gtgagaaggg ccacttccca 214200
gagaaagtgg gactgacata gaacctagat ggatgtcttg ggtactgata ggcaaaggag 214260
ccaggccggc tgttcagaag cycaggcaat agcataaacg aagtcatgga ggaaacaaaa 214320
atcattctgt gtacctttg tgtgtttttt ccattccatt ccctacgttt tgtttttttt 214380
agttttgagt atttaatact ttttaattta aattaaattg aattaattaa tttacttata 214440

tagacagggt cttgctctgt cacccagact ggagtgcagt ggcatgatta tagctcactg 214500
cagccttgaa ctcctgggct caagcagtcc cctgcctcag ccttctactt gcacaccacc 214560
atgcctggct tattatcttt aagaaaacag cttatataat tcacatatgg tatgtatggt 214620
atgatacaac ttacccattt aaagtgtaca attcactggc ttttggtata tgcagagttg 214680
tgtatccatc atcataatcg gttttaaagc atttttttcat caccctacaa agaaaccctg 214740
ttcctctgag ccaccatttt yctgccctca gtacctgcta atctgctctc tgtctctata 214800
gatttgccta ttctggacat ttcctacaaa tggaatccta cagtatgtgg ttctttgtga 214860
ctagcttctt tcacatgtgt gtcctttta atgaaaacca aacaaggtgg tatttaccag 214920
ttgttgagac tttaaaggcc cctggctgca ttttttccag agcccagttt gtctaaaatc 214980
cacacattcg tcagtagaat ttaaaacttg gcctatgcct gatgactggt ttagactaca 215040
ggctgcaaag cagcggctgg tgggccaaat atggyccata ggacatattt ggctgggaca 215100
acacagagct ttaagatttt tttttttta acatagtgct gacatttaaa atttaagaaa 215160
agaaagaaaa cctgtatttc ttgctttgga aatcagagga gcggattaca ctgggtaggt 215220
ctgccttcct gggcactgac aggagctctt acacagggtc ttgctctccg catcacttga 215280
tatttacaac cgggatctct cctcattcat cttacatacc tgttcctctc caggtatttg 215340
aaatcatgca atccctggtc taggtaattc aatgtgagat catctttgct tacatagacc 215400
cttgctctac aattaattat taattggatg caaaagacat atttaaaaag agttgctggg 215460
tgtggtggct cactcctgta atcccaacac tttgggaggc tgaagtgggg ggattgcttg 215520
agtccaggag ttcaagacca gcctgggcag cactggtcaa accacgtctc tactaaaaac 215580
acaaaaaact agccaggcat ggtggcacat gcctgtagtc ctagctactc aggaggctga 215640
gatgagagga tcgcttgagc ccaggagtgt agtgagctat gattatgtcg ctgcattcca 215700
gcctgggcaa cagagtagct ccatgaagat agaaatcttt gtatgttttg ttctctgata 215760
gatcccaaac acagaacagt gcctcttaca cagtaggcct tcaataatat ttcttgaaga 215820
gtgaacagct ttcataatac agctttcata atgcatttta aagggtctga atatccatcc 215880
ttcggccaat ttctattaag gaggtgcagt tttcaagaag gataaatcat atgtgctctt 215940
gygcccctat ttttgctccc catcttctgt aaaatataaa actggtgtca ctgagcaccc 216000
aggtccctga gataaacagt tggtttccct gtaggtaatg ccctgtgctc tgctgtagtg 216060
gagaagtctt aycaggtgag atgctacagt gaagaaatct tctgttatag gcttatgttc 216120
tggactgact ggggaaagga acctaaamtc gagtctgcct ggatgaatgg agaggaccgc 216180
aacatcctgg ttttcgagga ccttggttgg ccaactggcc tttctatcga ttatttgaac 216240
aatgrccgaa tctactggag tgacttcaag gaggacgtta ttgaaaccat aaaatatgat 216300
gggactgata ggagagtcat tgcaaaggaa ggttagaaat tarttagaaa gtaatatatt 216360
aaattaataa ttaacatatt tctaatgtct ttgcctgttt tctcaagaag gagccctgct 216420
cttaggaaat ggcttatata gttttttaga taccacccct ccacccccac caactcccac 216480
ctgctgaatt aaatgcagat gagttcatta gcaataatta aatccttttc gtccttttta 216540
cacaacttta aaaaaaaatg cttctcagca gaagatattg aaataactga gtttcctgtt 216600
aggttgcccc agtagaggtg gtttcatgtg taccaatgtt aattcatgtc taaccgcttc 216660
tggacacatt cattttcact ttactagatt gcccagtatg cacaactgta aatatctagg 216720
agatgaacat tttttgttgt tgttgttcag actctgcaga attgcaatga cccagcacat 216780
atcacatttt tcctatttgg tcagatagat gtcttatgtt caaaagaaaa cataaaatct 216840
tgccatttaa attgttttcc aaaaatgcag taaaatcagt aacttgaaag tgagctaggg 216900
ccctgtgatt ggtgtcgggt ggtatacatc aatgtggttt aatttctatc ttcttgacct 216960
cctaatgcag cacactttca cagtcccatg tagctaaagt cagcctgaat attcccagag 217020
cttcaaggca ttgtatgagg gaataattca agcagaatga catcagatct agaagtggcg 217080
gtagggtgta gtgggtattt tcttttcaat aaccttctgt tttgtttttc ccctgtgggt 217140
aagcagcaat gaacccttac agcctggaca tctttgaaga ccagttatac tggatatcta 217200
aggaaaaggg agaagtatgg aaacaaaata aatttgggca aggaaagaaa gagaaaacgc 217260
tggtagtgaa cccttggctc actcaagttc gaatctttca tcaactcaga tacaataagt 217320
caggtaatca ccaactttgg tataagatgc tcctcattac ttggaaatct tatttcaaaa 217380
taatggctat attgctggaa gatggcagta gataacaaca agctaatctc ttggtgcatg 217440
aaaggggtat atgtgtatgt acgtttgctg ggggagagga acgttttaac cattttmacc 217500
aaagaaagat aaaattggwg gtcaaatgaa attatgcaaa ccatcagcag gtaagtaaaa 217560
atattagccc tcatcattgt ttggagtgat ggatatgtac ttctaggcca cagaatccag 217620
cagacatcag tcccctgcta artgtgagtt gggttaacaa gtcacaaaat gggtttcata 217680
ggcatcagaa atcttatcct tcccattgca aggctaggct agtcaggtca acctgagata 217740
tgtaggtctt agtttaaaat ggccagtcat gtgcattcct acccgctccc ctctgtctca 217800
ctttcccact tctgggccct gcttcctcag gttacctgtg cgctaattta tccttcagca 217860
gtgtgtggag caagatgaaa ggcaaaggga agtgaggaaa ggaaatagcc ttttactaag 217920
ttcttrtgtc aaattctctc ttcagtgtta attcagccat ctattacttc aattacctta 217980
taaagacctc ccaaacctta taaagacatt ttattctcat ctcaaataaa gaaactgagg 218040
ccgagacaga tttagtaact tgtgtgccta agtcacataa caaatgggtg agttttaatc 218100
tcagaaatga aataattttt aggttcaatt ctatccaacc caaaactcag catcttgctg 218160
tattggccca gtgttcagta tgccaaagtc ccaggttgaa tgctatggat atgtggcctt 218220
tgacaagtta ctcccttcct gtccccatat gtgagtcatg ggtggagtcy ggggttgtct 218280
tgagtctgct gatattttga gaccttgatc agccttgaaa aattgcaact caaagctgag 218340

```
actcccatga gatgacaggg gtggcaaatg ccttttctag ggcatggctt ccttgttttg 218400
gaagtatatc accaaaacac tccagaatac tccagaccct accaatagaa tagcttttgt 218460
gtcctaagtg cccttgcggc tctcacactt ggcaatttta aaggtaggag aggaaggcac 218520
agtacacctg gaaaggctat ctcccctccc taccgcctct ggaccctgag gagaaggcag 218580
aggaaagtct ggaggctgcc cctgaaggaa aagcatctcc ctccggcagc tgatgctcag 218640
ggaaggcggc tcctttggaa agtgctggtg gagtgggggt gggggtgggg gtggggatgg 218700
ggagtacagc cccagcccag cctgtttgaa ccaagagttc tgaaagttga gcatgcctca 218760
gaattatctg gagagcttgt taaatataga ttcgtgggcc ccatctgttg cacttctgat 218820
gcaatatgcc tkaggtggcc taagaatttg catttctagt tctcctgtga cgttgatgct 218880
gctggttcag tgaccacatt ttgagaaccg ctgctccagt cccttgctac tcagagtgtg 218940
ggccatgggc caggagtctt gggatcctta tgggagctgg ctagaaatgc agtctctcag 219000
gcccacccca gaccttctga atcagaatct gcattttagc aagattcccc aggtgatkga 219060
tagcacattc aagtttgaaa atctccactc tggagggccg acgaaatggt aatgagacag 219120
atattgatgg aggcttttgg aagatgtgtt actaatttat agctatgctt tgtctgtggt 219180
tacatcttga atgacagaca atcaggatca cagaatgtta gtctgagaag gaatgtaaag 219240
attatccact ccagtacaac ccttggataa atcataatac atgctaaggt agaattaata 219300
aggctctaga cttacctagg gagcttttaa tggtaatact tgaactctac cccagaccaa 219360
ttcaaatctg aatctctgtg aatgggcatc aataggtttt tttgtttgtt tgtttttgt 219420
ttttgagacg gaatcttgct ctgtcgccct ggctggagtg cagtggtgca atctcggctc 219480
actgcaagct ccgcctcctg ggttcacacc attctcctgc ctcagcctcc tgagtacctg 219540
ggactacagg tgcccgccac cacgcccagc taatttttt tttgtatttt tagtagagac 219600
gaggtttcac tgtgttagcc aggatggtct cgatctcctg acctcgtgat ccgcccaaag 219660
cggcctccca aagtgctggg attacaggtg tgagccaccg cgcctggcct ggcatcaata 219720
gttttgaata gctcccaggt gattatgagg aaccattgct ctaaattccc ttttcttgca 219780
attaaggtaa ctgaaaccca gaagaaatgt ctccttggag ggttggggtg gaaatcacat 219840
ccagtatact ttggatagac catatgttat gatctgtcca gttttgggta gtgacaaatc 219900
ttggtayaat atgtggatct cactggtctt ttgaaccatc kcaagttgtt tagcactgag 219960
tagattttga ggttaggcag tgaaccagat acccaccttc caaacctctc agggcagcag 220020
agaagataag tgatgccaat agaaaatgtg agtggtacag aaattggctg gagggcccag 220080
agagggacta tcccactgca gtgtggtggc agagatgata gtgtaaatga gggtgagtgg 220140
ccagctgaca crtggaygag aggtattgag aggatgccta ggctctgctg tcacctggca 220200
gagccacttc cagttgctgg gtattcaggt tattcattct gtcaggacct aactgctgtt 220260
ctcacccgct ttccagtgcc caacctttgc aaacagatct gcagccacct ctgccttctg 220320
agacctggag gatacagctg tgcctgtccc caaggctcca gctttataga ggggagcacc 220380
actgagtgtg atgcaggtag gagcactgcc caagcagcta tgggggcctg ggagcactcc 220440
tctgctgcct tcaggagtca gaagaatccc tgtatgctgg gtcctttgca gcagagtggg 220500
gatggctgga aggagggtta agggatgtgg gaggtatgaa cagagttgag tgggacttag 220560
ggggcaaaca gaactgtgtt ccagtgactg ctgagaatta tttgctaaga tctgcagaaa 220620
tatagatcca gtgtccctaa atctattgct gtgttgtttt gtaaagacat tttgaagagt 220680
gagtttttat aagacctcta cctcaagctg gattcccatt gccccagaat ccactcaacc 220740
ttaattgtag ctcctcaggg tagagaacca tgtycagttt tgacaactga aaaagggcta 220800
ccttttgaaa agtgctttat attatcagga gacgaagacc agcatgagga agctgtggtt 220860
taattctagt cccaaacgct gtgggtgatc tattcttggc aagacttttt ttcaatgact 220920
cttttaagga gttaataagc cggatggggg cgaataacta gtgtccctaa ctagcatccg 220980
gtgctggaaa agcctgtgaa aaagtcgtcc tgcaattcac tagcggccca ttttatggct 221040
cacatccttg gggccttccc ccagttttag ctgatgggga aaggaaaacg cttaaccacc 221100
ttctaccacc aggggggagca ggcagttaga ccaggaacca ccctttgact cattccaaac 221160
aggctgagga gttggcaggt ttagggaatg aatccaggga gaaaaaactg tttcttgtca 221220
cccctcttcc cctactcttg cactcatccc aacgctactg gggaaatatt ggtaggaatc 221280
caatatttcg agccatattt ggaacaaaat gacaatttca ggctttgaga tttgttccat 221340
gctgtggata gattgttttg ccacttactg caatttcaca tcgtgggagc agtgtggtcc 221400
tggttgtcac ctcatctact acttttctca tttaaacttt ttgccaagtg gattttatta 221460
agattcttgt tttaaagaac tttaaccgaa gtaagcacac gaatgatggc agtcattcca 221520
tatagggcct cggtttggta taataattaa gcaattagtc cagtgagatt tcttgagtgc 221580
cagctatgtg ccaggcactg ttctaagtgc tggaggtaac agaggtgaac aaaacagaca 221640
aaacccccctg tgtgtattga gtttacattc taagaggaca ataaatagag aagtcaataa 221700
atayatggta gttcaggtgg tactatggag aaaatgaagg cagaggaaga gggatgagga 221760
tggggtgagt ggggattgtc ctttagatag tgttcaggga agacctgtct gatacagtga 221820
acattgagtg gagactcaga ttgaaggact gagccaggag ggtatctaga ctctttaaat 221880
aatatacaca tgtaacctat acttattaag catcttcaat ataaaagaca ctgaagcact 221940
aattccccat caggcacayc ctgggagtat gtacaggcct agctgggagc agggacttgg 222000
agtaagggca gtttgggagg acttgaaaac tcaggagctc tctagctaac tgcctatcaa 222060
atatctctat atctgtagct atgtgactgc ctgtggactg atcaattact gatgctttgg 222120
tgtctttagt tgaagtttca aggtgggcct acattaaact cttgatttta actgggttca 222180
yggaggagaa ttctgaaaac ttcaaatgag aatgtgaata ttttaagaga ttattttacc 222240
```

actaggttct tgtaactatt aatatatgtg ctccagagtc tagtacctct ccattgtttt 222300
ttgggaaaaa ttctataaac tgcccccttt ctttccacta aatgtatgtt actctccaag 222360
accttaagga aactcactgg acttaggggg aaggtaagct ttgacaggga gactaattgg 222420
ctggcctgcc cctcctccca cccctaacct gggccggttt gcatggtgtg ggcactctgc 222480
tgagtacagc tgactaacac ctgcatggct ttcccttcct gcagccatyg aactgcctat 222540
caacctgccc cccccatgca ggtgcatgca yggaggaaat tgctattttg atgagactga 222600
cctccccaaa tgcaagtaag tctgaatgtt gaggtcccrg ctataggcct tgcctcttct 222660
ggggaaattt gagaccttaa agtagccagg aaaacaaata caggaacctc accagttcac 222720
taattcttac attttaacca gcttgccttc ccttgaggga gtctacagag aactgaggca 222780
gtgcttcttt aactagaatg tgcataagaa tcccgtggag atctggttca agtgcccatt 222840
ctcacgcaca gagattctgc atttctaaca agctctaggt aggccacagg gtcttggacc 222900
acactttggg gagcaaggag ttagaraatt ggcagcagca ttttcctact cacctggtat 222960
tgttgattac aacagggctg tgggagaaga gctgtctgca gggctgcttt agtacaaggc 223020
actsgtgatg agcagaaaga ctgggatgga ttcggaaaga agatgactgt gttgcgaaaa 223080
ctctaacatg gagcaagata aatggatgtc tttaaaaagc atttaatgaa agcatataaa 223140
agaaagaaac ataaccatgg tttccatttg tactctctaa ggaagcattg catagattag 223200
acaccaatag gttttcgtgg ccagactcac cccctcagtg ccacagctac tccattacaa 223260
gtgcatttct aaaatcagag cactgttctt tctgcttgtc ttctcttggc agaatgaaca 223320
aaagtcatgc aggatacatt gtctgttcaa catgtaattt atgcagtcaa agctctctct 223380
acttcaggat gtgctcagaa aaatgcagta gaagcctaag awcataacag ctagtgaatg 223440
atttgctttt tcctttcagg tgtcctagcg gctacaccgg aaaatattgt gaaatggcgt 223500
tttcaaaagg catctctcca ggaacaagta agttttaaga atgtgagcaa cttggaaatt 223560
actcatggcc cctacattga atgctgtcac agcttttcta cttmacccag tctttgaagg 223620
agtggttcta gcccccagtt tctgccagga ttgcgggctc ccatgtgttg atgtgctctc 223680
tgctatcttc ttctatagcc gcagtagctg tgctgttgac aatcctcttg atcgtcgtaa 223740
ttggagctct ggcaattgca ggattcttcc actatagaag gaccggctcc cttttgcctg 223800
ctctgcccaa gctgccaagg tcagtttcat tatggggaac gttgatgttt gaagcctaag 223860
aaattcatat gaagccatgt gaaggactta gttttctttc taagttaaaa aagcacaata 223920
cgcagttcac cgattccaca gaaacaaaaa gtagtgagga tgtaaagcag tcacttcaaa 223980
tcccaacttc ttagtcaart gcttctctaa agcctgagtg acaagctgtg ttttgtagtc 224040
caaatggttg tgcctactgg taggtgttca ggtcagagag gagtgaaaag gcagctgtgt 224100
gatggcccag gctttatcct tctatgtgct ggactctttt tcttttagat ctcatggttc 224160
aggaatgtgc tttaacgttt ccaggtagct aagggaactt actaccatat ttgacagtgt 224220
aaatttagag tgggaattga gcattacatt tgaggaagat ttggcaatgt ggaggagagg 224280
gtactattgt gaaaggttgt atttgttgtt tttgttgttg ttgttttaaa taacaagaca 224340
ctgttttggt tacttctttc cagcttaagc agtctcgtca agccctctga aaatgggaat 224400
ggggtgacct tcagatcagg ggcagatctt aacatggata ttggagtgtc tggttttgga 224460
cctgagactg ctattgacag gtcaatggca atggtgagta tggtttcaaa atgattattt 224520
gaaggttgtc atttatagaa taaatacttt ttataaagaa caaaattcac ctagagaaga 224580
ctgaaataca gtattaggcc tctcagaata aggtctgcac tacacaagtt aggaaacatt 224640
aggtttgttg ctgaaaggtg tctaaaaaca ttggtaataa cattggaatt tacccctgct 224700
ctaagccacg ctgttgaatt ggaatcatga acagtctgaa gtttaacttg aatattgaag 224760
agctttctgg ttttttgag ggtggtgtgt gaggaggaca tgatattttg tttttatttg 224820
atgactttta tatgtataaa aggagtaggg aactatattt ttcctagtgt catatatttt 224880
tctgccaatg tatagtgatg aaataaacag tgattttaga gttggcgttg gtccagacca 224940
cggctctgcc acctactaag tatgtgacaa tagacatgga gcttgatatc tctgaccctc 225000
attgtcccta tttgtaaaac aggtaaaata atacctcctg ggaggaccaa atgaaatact 225060
ttatgagggg gctgccacag tcttggcact gaggggggctt tctgtaatca gtattgggaa 225120
accactttca gaattttgtc tctccctcaa atctttcatt gttttccttc cctgagaata 225180
ttatattatc cattcttttt ccttcccctc tctccttatt cttcttttct tcttccacca 225240
ttatcctttt ctctgtggcc cagacccaat tcccaagtga gttatttaag agaatttgga 225300
tataagaaga atgttaccat ttccttgagt tggtaaatta gtgcatgtta tgttactttg 225360
cataatаatt tgccatatgg aggtcttgtg ttttgctggc ctttttttтt ttttttttтt 225420
gcaagttctc ttttgggtaa cttatgacgt agcacctagc gtacctccag gtgtgaggaa 225480
ggcacctttc tttgtgtgtg aaccagatta gtatggtgta atctctctct stgtttctct 225540
ctctctctct ctctctcttt ctgtctctgc catcagagtg aagactttgt catggaaatg 225600
ggraagcagc ccataatatt tgaaaaccca atgtactcag ccagagacag tgctgtcaaa 225660
gtggttcagc caatccaggt gagaaaccat acagtctttt ctttcagtta ctgctgtcgc 225720
tggatcttaa tctattgagt catgtcttag gattttccta accttccctc caaagggaag 225780
gaagcatagt gagtggtcca tgctgcagct gccctatctg caggaacagg accaacccaa 225840
ggacataaga cctgaaaaca atcagaatcc tgttctgttg cacagtggtg gaggtttggc 225900
agccatgccg gggctgctgg ccaagaacct ttcattttga gtggtgtcag agcaagagag 225960
gtctgagtcc cttcaggggc ctgggaaaca cagtgcctga agcaccacag cttctctaca 226020
aatacttgtg aaatgaatga gtggagaatt gtcaggtcac tatacaggaa tttggggacg 226080
gggcccactc tctggttctt gctgctatcc caagcatgtg gtttgaggtg gattaaaggg 226140

agagggacct cttatgcttg ctgttgccat acttttctga aaagtacaaa ggtctctaga 226200
gttgatgggc agatatctaa atttccttgt tgcagccttg ttgctcagtc atctttttt 226260
gtgtgtgtga gcaacaaggc tatttatttc acctgggtgc aggcgggctg agtccgaaaa 226320
gagagtcagc gaagggagat aggggtgggg ccgttttata agatttgggt aggtaaagga 226380
aaattacagt caaaggggggg ttgttctctg gtgggcaaga gtgggggtca caaggtgctc 226440
agtgggggggg agtttttgag ccagatgagc caggaaaagg aatttcacaa ggtaatgtca 226500
tcagttaagg caaggacmgg ccattttcac ttcttttgtg gtggaatgtc atcagttaag 226560
gcaggaacag gccattttca cttcttttgt gattcttcag ttacttcagg ccatctgggt 226620
gtatacatgc aggtcacagg ggatgcgatg gcttggcttg ggctcagagg cctgacattc 226680
ctgccttctt atattaataa gaaaaataac ataaaatagt attgaagtgt tggggcaaag 226740
aaaaaaattt ttgggggggt ggcatggaga gataatgcgc agtgtttctc agggctgctc 226800
aagtgggatt aggggcggtg tgggaaccta gagtgggaga gmttaagctg aaggaagatt 226860
ttgtggtaag gggtgatatt gtggggttgt tagaagaaac atttgtcgtg tagaattatt 226920
ggtgatggcc tggatacggt tttgtatgaa ttgaaaaagt aaatggaata agagaaggag 226980
aaaaacaggt attaaaggac taagaattgg gaggacccag gacatctaat tagagagtgc 227040
ccaaggaggt tcggcatagc cctgccagca aagattattt atttacttta agagggagtt 227100
aagagtggcg gtttggggat agcaccacga gatatcagct gtgacggctt ggagaaacag 227160
tgtaaaccgg tggtataaac aagagcaggg catttatgag tagttgagaa cggtgaatag 227220
gagtatgact agacagaaga tagtagggat gacaagtttt ttggggtgca gtccaagttg 227280
gtctggtgtc tggaatgaga ctggggctta ataaaaagga gcgtctatac aggagcttaa 227340
atggctgtac cctgtagcat tctgaggaca ggcctgaatt ctgagaaggg caagtggtaa 227400
aagtattgtc cagtcctttt taagttggtg gctgagcttg gtgaggtgtg tttttaaaag 227460
accattagtc cattctacct ttcttgaaga ttgaggaccg taaggggtat gaaggttcca 227520
ctgaatacca agagcctgag aaactgcttg ggtgacttga caagtaaagg ccggtccact 227580
gtcggactgt atagaggtgg gaaggccaaa ccgaggaatt atgtctgaca gaagggaaga 227640
aatgaccgca gtggacttct cagaccctgt gggaaaggcc tcttcctatc ctgtgaaagt 227700
gtctacccag accaagaggt attttagttt cctgacttgg ggcatgtgag taaagtcaat 227760
ttgccagtcc tgggcggggg aaaaaccccg agcttgaggt gtaggkaagg gaggggggcct 227820
gagaaattcc tgaggagtag tagaatagca gatggaacac tgagaagtga tttccttgag 227880
gatagatttc cacaatggaa aggaaatgag aggttctaag agactggcta gtggcttgta 227940
acctacatgg aagaggttat gaaatgatga cagaatagaa tgggcctgtg aggctggaag 228000
gagatatttt ccttggtcta agaaccattt gccttgtgtg ggaagagatt gataggtgga 228060
agtttcagcg ggggactagg tgggagtgac taatgtgaag gagaaaaact gacygtgagg 228120
gacagaagtt ggaacgctag ctgctttttt agctaattta tcagcataag cattgtcctg 228180
agcgatggga tctgatgcct ttttgatggc ccttgcagtg aatgactcca gcttcctctg 228240
gaagtaaagc ggctttgaga agcgttttta ttaaagacgc attaatgata gaggaccctt 228300
gtgtagtgag gaaacctctt gcatggtggt gcaggatatg gaaggcatat atagagtcag 228360
tataaatact gacatgtagt ccctttgcaa gagtgagggt ttgacttaag gcaatgagtt 228420
cggcttgctg agaggtagtg gagcggggca gagcggtagc ctcaatgata gatgtgsaag 228480
atactatagc atagcctgcc tttgctggtg agtggcgatt aggcctggtg gaactgctat 228540
cagtaaacca agtgtgttca gggtgaggaa caggaaaaaa ggaaatatgg ggaaatgggg 228600
tgaatgtcag gtggatcaga gagatacagt catgggggtc aggtgtggta tccgtagtaa 228660
tgtgggaggc tggattgaag tctgggccag aaacaatggt aattgtggga gactcaacaa 228720
agagtgagta cagctgaagg agctggggaa cagacagtat atgcgtcagg tgggagaaag 228780
aaaatagatt ttggaagtta tgagaactgt agagagtgag ttgagcatag tttgtgattt 228840
ttagggcctc taaaagtatt aaagcagtgg cagccgctgc acgcagacat gagggctagg 228900
ctaaaacagt aaggtcaagt tgtttggaca gaaaggctac agggcacggt cccggctctt 228960
gtgtaagaat tctgactgca ctaaccatgc ctaggaagga aaggagttgt tgttttgtag 229020
aagggattga ggtttgggag attagtcaga cttgatcagc agggagagca tgtgtgtttt 229080
tatgagaatt atgccgaaat aggtaacaga tgaggatgaa atttgggctt gactgaagta 229140
atgggggctg tctgtgaagc tttgcagcag tacagcccag gtaatttgct gagcctgatg 229200
ggtgtcaggt tcagtctaag tgaaagtgaa gagaggctgg gatgacgggt gcaaaggaat 229260
agtaaagaaa gcatgtttga gattcagtcc gtcatcttta agaagagctg ggagatgaaa 229320
taggaatata ggtgaaggga ataactttac ataaggtctg catcaatagc cccagcgcca 229380
cttttactgc ttgtcaactg cgaacatgta tctcctttgt cacaacaact atggccttag 229440
tgacaatgaa taactgtcat tgttaacacc taatgctcct tttgaactcg agatatggca 229500
cattttaata cagaaactag aaatgtttat tttacaaata ttttgtgatt ttaagatcgg 229560
aaatgtttaa atcttgaaag cattttccct gatcctctga taaacagata tgaaaacttt 229620
aatcacatga taaaagagat acgacatttc atttgacatc ttcacttaaa ataaaatgag 229680
gccatgtata caaatgcata tccaagtttc agaataaaca agtaatgaat gtgaaaatat 229740
aggaaaagga gtgaattgtc taccttgtag tttattatgc attcatggta atttggtctt 229800
aaaagggaac cttggaattg tatgaatgtt atagaaaaat gcgtagaaga ttattaattc 229860
tatcattctc atcttttcaa aaattcaacc tctttttagt agtactatga aatcttaatt 229920
tccgaagata ggatttatta atattcaaag aaattattaa gatccaaaga taggattctc 229980
agttcatcag tgaggttggg gaattattct tgctgttctt ctaggatttg gcttccagta 230040

tataactaga gtatgattat ccaaaaattt ggtcaacagt gggagtaaga aggtatagag 230100
aatacagtag aaattgctag taataagtga gagtgtgacc agtgagggat gtatttgcct 230160
cccaggatta aggtatgagg tgacttagtg gttgctgctc ttgattttgg ggcggtggga 230220
gtgatgttta gtcctggcct actgggtcat gcaataaaaa tggtgcctga tgatgtctgt 230280
gggagaacaa gatggcaaaa agagccagag ttggtacaaa ctttacagca aatttattta 230340
ctactaaatt ctttcaaaat tgggtaaagg cctttaacat gtccacaggt gactgtatct 230400
gaaaatgtgg ataataagaa ttatggaagt cccataaacc cttctgagat agttccagag 230460
acaaacccaa cttcaccagc tgctgatgga actcaggtaa cagttgccga ctcctgaaat 230520
aatgtgggat ttggaaaaac tttgggatga ctgggttttt attamcctta agcaaacaag 230580
ggagattctg gaaggctcaa agatctcaag atgtgttgac agttaataaa tataattttt 230640
taaaaagtca tagattgaaa aactttccac caaataaagc tacattctaa catcgagttg 230700
ggaataatgt tccttgtaac ataggaggac atgtcacaaa gaagaacaaa tagacttctg 230760
gatccagtat cttcagacca gagacattta agttgagaaa ttgactcagt atgaataaag 230820
atttcacggt gtcaaagata cagatgaaag atccgtctgt gtgtgccgtg atttctctac 230880
agcatgcatc tttattcttt caagctgttc ttcgctctcc tgctattaca gatctttacc 230940
actagatggc actaattttt ccattcatca tccatctatt cattattggc caaccaatca 231000
tctaactaac gttattcccc tcgatgtgtc agggatggtg tttaatactg gagattgaaa 231060
gaaaaaaatg ccactagatg gagcttctta aacatgcctg caggtccttt gcaattggta 231120
cactatttgg tctgcaggaa gaaattcaat aaatatattt gatattaaac tctgtattaa 231180
tgtatatcat tagttttaat gaatgcatwt gcagctatac cagatatagc tgtttgaatc 231240
tggacaaact gttttacttc tggggctaga gtcctcaata atatttctca ctgggggcgc 231300
tattggcata ttgagtggga cagttctttg tgctacaaaa ctgtcctatg cactcaggga 231360
atttcagtat ttctggtccc tgtccactaa attccagtag tgtctcccct aattcagtgt 231420
gaccccagaa atcacctccc ctccccaaca catgtgcact cactcctggt tgagaaccgc 231480
taggatctgg aatgtctctg ttctaagatt ctatgaccaa ttttgtgaag taatgtaaag 231540
aaatgaaagt ctaagagtag ttggaaattt taccatttta tacaatcttt atttctcaaa 231600
tttcatagtc tataaacatt gatatcttgg taacttggca gtctcattat caccttaaac 231660
attggtttct gttctgctga tttaaatcaa aataaaattt gacctaaatt gatgctgaga 231720
agagtctata tcaaggcttc tgtacacctt ctcaaattcc cttatttctt cttctcatgt 231780
cacamacaca cacacacaca cacacacaca cactcataca ctcacagaca tacataaata 231840
ttgtctagaa aggaattttc agtttcagat ttttcaaggg actaaacatt ttttctttaa 231900
gctrtattaa aaatggattt tgaagattaa ttttccacag acacacggat gcttgaatgt 231960
catatatytg gtcctccaag cctgagtcaa ccccaagcta gtgccagatt tattttatat 232020
tttcaacatt ttttctcagt ccatctctag tctagtgatc ttcttcacta aatagacatt 232080
ttccccagct ggtgcaggaa ggggactgtg gtggggaggc tgtaacctct gatctgcatg 232140
tctgttatca gaaacaaaat gtaaactgac agtctctttc aaaggagagc agatcttcac 232200
caattgtagt cctttctttc tcttcccttt tgtaatacct tggttcctcc tcttactttt 232260
ttacattagt gaggctgaga ccctctaaaa tgtgtcttcc atgttatgtc cagggatctc 232320
actgtatttc ttccctcctg ggcactgagt taacagccag catgctttaa aagcagtaga 232380
ggcgcttggg tgagatcacc taggttgatt tgaatatgcc agagtcccac aaatgtatct 232440
ttcatccata aatatgttga aagactaaca attaaaaaca tgggctgggc acggtggctc 232500
acacctgtaa tcccagctct ttgggaggcc gaggtgggtg gatcatgaca tcaggagttc 232560
aagaccaacc tggccaacat agtgaaaccc catctctact aaaaatgcaa aaattagctg 232620
agtgtggtgg catatgcctg tagtcccagc tattcaggag gctgaggtgg gaggattgct 232680
tgaacccggg aggcagaggt tgtagtgggc cgagactgtg acactgcact ccagcctagg 232740
cgacagagtg agacttcatc tcaaaaaaaa aaaaaaaaag attcagttct atcattttcc 232800
aaaagttaca ttgatatgca taggatcccc caaggagaca aaaatgaaag tcaccgtccc 232860
tttcctcttg ttagtaattg cttaacttca agttagccat ttcattttga agcaatgaca 232920
tctaagagac tttggcccgc cccacttaac tgtaagcgcc cagaggcagg gctctgacct 232980
gaatgtcttc atgttcccct tgggggcact atgtacaaag caggttctca cttgaatgtg 233040
ggttaaagtg aagacctctt ctacttctgt agccctgtgt tccccactcc tccacaggct 233100
ggtcccctgc tgtcacagag taagagacac cccataaaac ctgtgggctc cctcagctcc 233160
tgttgagagt aggctgtctg ttcccttgtc tcccaccagg tttttatctg gcagtcagca 233220
tgacaggcaa cttttcagta aagcgtgggc cacgcaccat ggtccagggt gattatcttt 233280
gggttctcca gtttatgggc ctctgggtcc cctgagtaat cattacctgc ccttctacct 233340
gcaagttagt tgtataatct tgctgtgact cagcaagtat aggataataa gtgtacctac 233400
ctctggggtt tgttaaaaaa aatcagaaac ttgtaaaact cttagaatag ttcctgacac 233460
atagtaagca ctcaataaat gttagatgtt tttgttatta ttattgtgac acaggaggga 233520
atgatgaagg gagaagggat actcttgagt tgaccaaaga atgttacttt agggaataag 233580
agttacagtt tggctttgcc atctccaccc aattttcagg cagccccaga aatctctttt 233640
tctccagatg catcttgtgc atgtctgttt tatgtgttct ctctgtactg aggtaaccag 233700
gtgatttgct tgtagatact atggcacaaa ttctataata tataaatttg aagtcaaaga 233760
agtgtttaaa accattcgat taaaagagcc cagagtttca gttactgttc agggaccata 233820
ggaggaattg aacaatttac catatgggct gaatcacatg gtcccaggtc ccaaattgct 233880
ttacccttca gtaagaagaa attttaaaac tgagacagga ggaaaagaaa cccacaaaat 233940

aattccatta ctgagaggtt tttgttttcc ccttttcatt taggtgacaa aatggaatct 234000
cttcaaacga aaatctaaac aaactaccaa ctttgaaaat ccaatctatg cacaggtaat 234060
ttttaacaat ttttcttagc acagacattt tttcttagaa attatttgct tggttaaatt 234120
ggacacacac ttagattatt ctgagcagag tggccacaar tagtcttctt tatgaaaaac 234180
cgtgtatggt gaccttgggg gaataaatgg ctgattcctg ttacattgta ttcttagatr 234240
gagaacgagc aaaaggaaag tgttgctgcg acaccacctc catcaccttc gctccctgct 234300
aagcctaagc ctccttcgag aagagaccca actccaacct attctgcaac agaagacact 234360
tttaaagaca ccgcaaatct tgttaaagaa gactctgaag tatagctata ccagctattt 234420
agggaataat tagaaacaca cttttgcaca tatatttttt acaaacagat gaaaaaagtt 234480
aacattcagt actttatgaa aaaaatatat ttttccctgt ttgcctatag ttggaggtat 234540
cctgtgtgtc tttttttact tatgccgtct catattttta caaataatta tcacaatgta 234600
ctatatgtat atctttgcac tgaagttgtc tgaaggtaat actataaata tattgtatat 234660
ttgtaaattt tggaaagatt atcctgttac tgaatttgct aataaagatg tctgctgatt 234720
tggttggtga tcattatagt aaatgatcca acaagaaaag gaattgactg gggaccttta 234780
gccgtgtcta aagaagaggc accactcata tttcctataa aattatctag gaaaggaatc 234840
caggccccgc tcttgggtcc atttttacac attagcactt aattaatgtt caatattaca 234900
tgtcaatttg attaatggct atgttgatag gggccactat gtgttgtata gacatctgga 234960
cttgactgta gactcctcag ataatacaga aggtaggaaa agcaattcag tttggccctt 235020
ctgtgtgttg gcattgtcta accagaactc tctgtttcat gtgtgttctc tcactagctg 235080
ccaagacaac atttttattt gtgatgtcta tgaggaaatc ccatatcatt aagtgccagt 235140
gtcctgcatt gagtttgtgg ttaattaaat gagctcttct gctgatggac cctggagcaa 235200
tttctcccct cacctgacat tcaaggtggt cacctgccct agtagttgga gctcagtagc 235260
tgaatttctg aaaccaaatc tgtgtcttca taaaataagg tgcaaaaaaa aaaaatacca 235320
gttaagtaaa gcctcaactg ggtttttgtt tctatgaaaa tatcattata atcactattt 235380
atttcctaag ttgaacctga atagaaaggg aaaccattct tattaagctt tttattaggc 235440
cctgtggcta aatgtgtaca tttatattar aatgtactgt acagtccaga tcttttcttt 235500
aattcttatt ggtttttttt ttttttttt ttttagagat ggagtcttgc tatattgcca 235560
aggctgatct tgaagtcctg ggctcaagtg atcctcccac ctcagcctcc tgagtggttg 235620
gggttacggg cgtgagccac tgtgcctggc ttccagctct cctcttaaat agtgggtata 235680
gtctgcacaa caggaaccat ggcaggaata tacactttcc catagcaaat agcatacctg 235740
actctctgtg ctaatattgc acatttgtta aacaatgaat gaadggatgg atggatggat 235800
ggatgaatgr atgaaacata tactactgat tattttattc cagagttctc aaaatatttg 235860
ttgctgatat tttgagtgct gactgtaatt actttgatta gataaacaac tggaaataat 235920
gctgctgaaa aagttctaat aaatgtgtat tttatcagat gttttctgtg tgcttcataa 235980
gccccagtca tgaatcagtt gtattttgct gtgtaaaaag cttgaggctt tgagtgctct 236040
tagtcacacc aattctgtac cactccttct tggaattgaa tccagagcaa tttgattgaa 236100
aatcaagcct ctgcattcat ttttttgtgt gtccatgata ttctggggta agttatagga 236160
aacaaataac tctccagaaa tgagaagtta tcagagtcgc aggtaaccac cagtatagcc 236220
agtccttgaa tgctgtccat ggctaaggca gagcagggag gaaaggtgca tattcctgtt 236280
tctctaataa ctagcgttcc cctaacagtc atttgtcaag aggacaattt cccagccagc 236340
tccgttaagc atagggtatg ggccatcttc ccactgttaa tctctctgag cctcagctgc 236400
tgcctctata aaatagggggg ctcggttgtg agaccccagt gtgggagtgt aacccaacac 236460
ccagcataaa atataccttc aatcaatgga agccatgact attatcattt atgaagtaaa 236520
gggaaaatgg aacagccatt tgtgtgtttt aaaaagttcc ttgggtcatt taacgaagag 236580
ccttggttga aaatgacgat tctaaataga aatggctgct ctttcttttt tagtggagga 236640
ggttacagag gtgaacaaga ttgtgtctgg gcctttgaaa ggattaacac gtatcttgtc 236700
tataatgagg ctgaagagca gatgataaaa agtttggtct tgctttactg tcatttgaag 236760
gtgataggaa gggcagtaaa cactcctgta catagaaatg ggaaaaggtt gagaagacgg 236820
aagtgcatat tcacatcaca gcacagggaa ctgaggcacc gctgaaataa atataccttt 236880
cccagattcc tccaaggatc ccgaggagtt gtttgagttt gttgtatata ttctggatat 236940
gagtcccctg tcaagtgaat agtttgcaaa aattttcttc catttaacag gtggtctctt 237000
cattttgttg attgtttcct ttgctgtgca gaagcttttt agtttatcat aatcccattt 237060
gtctattttt ggttctgttt cctgtgcttt tgagttctta gtcataaatt atttgcctat 237120
aagaaagtcc aggagagttt tccctaggtt tttttctagg atttttataa ttttgggtct 237180
tacttttaag tgtttaatcc attttcagtt aatttttgta gatggtgaaa agggtccagt 237240
ttttttcttc tgcatgcagc taccgatttt cccagcacca tttattgaag aggatgtcct 237300
ttcccccgtg taggttcttg ttagctttgt caaagatcaa ttggctctta aatatgtggc 237360
tttatttctg ggttctctat tccattctgt tggtctaggt gtctattttt ataccaatat 237420
catgccattt tgattactat agccttgtag tcaggtagcg taatgcctcc aactttgttc 237480
ttttgctca ggattgtctt ggctattcga gctctttttt ttggttccat ttttaaattt 237540
tttttctaac tgtgaagaat ggtattggta ttttgatggg gattgtgttg attctgtata 237600
ttgctttgga caatatagtc attttaacaa tattaattct tccaacccat aagcatggag 237660
tatttcgcca tttgtttgtg tcctcttcaa tttatttcat cagtgttttg tagtttttct 237720
tgtagagatt tttcacctcc ttaaatttat tcctaggtat ttttttttgta gctattgcct 237780
tcttgatttt tttttctcgg ctagctcatt attggtatat agaaatgcta ctgatttttg 237840

tatgttaatt ttgtatcctg ctacttgatt aaattcattt atcaaaccta ggagtttttt 237900
tggtggagtc tttagattat tctggataga agatcatatt atcatcaaag agggacaatt 237960
tgacttcctc ttttacaatt tggatgcctt ttatttcttt ctcttgtctg attgctctag 238020
ctaagacttc cagtactatg ctgaattggt taaaagtggg catacttatc ttgttccagt 238080
tcttagagaa aattctttca acttttctcc attcagcaca acgttatctg tggatttatc 238140
atatatgttt tttattattt tgaggtattc ctagtttgtt gagagttttc attctgaagg 238200
gatgttgaat tttatccaac gttcttttct gcatctattg agatgatcat atggttttgt 238260
tattcattct gttaatgtga tgtatcatgt ttattgattt gcatgtgttg aaccatcttt 238320
gcatccctgg tgtaaatccc actggatctt ggtgtattat ctttttaatg tgctgttgga 238380
ttcagtttgc tagtatttta ttgaggattt ctgcatctgt gttcatcagg gatattggtc 238440
tgtggttttc ttttttttgt tgtgtccttg tctggtttgg ggatcagggt gatgctggcc 238500
ttatagaatg aattagggag agttccctct tttttggaat catttcagag ggattggtat 238560
tagttcttct ttgtacgttg ggtagaattc agctgtgaat ctatccagtc ctggactttt 238620
ctttattggg agacttttta ttatggattc aatcttgcta ctttttattg atctgctcag 238680
gttttctgtt tcttcctgat acaatcttgg taggtagtgt gtttccagga atttatctat 238740
ttcctagatt ttccagtttg tcagcatata gttgttcata atagtttctg atgatctttt 238800
gtatttctat ggtatcagtt gtaatgtctt ctttttcatt tctgattttg tgtatttggg 238860
tcttttcttg gttagtcttg ccagtggttt atccattttg tttatatttt tgaagagcaa 238920
ctttcatttt gttaatgatt tgtatttctt taagcctcta tttcatttag ttctgttctg 238980
atctttatta tttcttttct tttgttcatt tggggtttgg tttgttcttc cttttctagt 239040
tccttcaggt gcgttgttag gttgttagtt tgtaattttt ctacctttt gatgtaggca 239100
tttaatgcta taaacttctc ttttaacact gcttttgctg tgtcccacag attttgatat 239160
gttgtgtttc cattttcatt tgtttcaaga aatgttttta tttccttctt aatttcttta 239220
tttacccagt ggtcactcag gagcatgtta tttaattccc atgtatttgt atagtttcca 239280
aaattcctcc tggtactgat ttctagtttt actccagtgt actctgagaa gatacttgat 239340
ataattttga tttttaagaa tttgttgata cttgttttgt ggagtaacat atggtctatt 239400
ctgaagaatg ttccatgtat tgatgaaaag attgtatatt ctgtaattat tggatagaat 239460
gttctgtaaa tgtctgttag gtccatttgg tctaaagtcc agtttacatt taatgcttct 239520
ttgttgactt tctgtctaaa tgatctgttt aatagagtgg gatgttgaaa tcccccacta 239580
ttattgtact gcactctatc tctttatatc tagtaatatt tgcttcatga atctggctgc 239640
tccagagttg gatgcatgtc tgtttagaat tgttatgccc tcttgctgga ttgatccctt 239700
tatcaacata taatgacctc ctttgttttt tatttttgtt tctgtttttt actgttcttg 239760
ccttaaggtc tattttatct gatataagca taatactcct gcttgctttt ggtttccgtt 239820
tgcatggaat atgtctttcc atccctttac tttcagtcta tatgtgtctt tactggtaca 239880
gtgagtttct tataagcaac atatagttgg atcatgtttt taaatccatt cagccattat 239940
attttcggaa tttaattttt ttatgttcaa aattattatt gatatgtgaa gctccattcg 240000
ttcctgtcat attgttagtt gttttctggt tgttgtaaat attctttgtt ctttactttt 240060
tctcatattg attgtcattg tagtttggtg aatttctgta gtggtaccat tgagtccttt 240120
ttcttccttc tttatgtgat tactttacca gtgaatttta tatgtttgtg tgttttcatg 240180
atggtaaata ttgtcttttc acctccaggt ttagaactcc cttgagtatt tcttataggt 240240
ccagtccagt ctagtggtaa acaaattctc tcagcatttg ctgtgtggga aagactttat 240300
ttcttcttca tttatgaagt gcaattttgc tggaaattgt atcctcggct ggcaggtttt 240360
tgtttttttg ttttttttct ttcagcactt tgagtatgcc atcccattct cttctggcct 240420
gttaggtttc tgctgagaca tctgctgtta gtctgctgag ggttactaga tagattacta 240480
gatggttttc tcttgctgta tttagtattc actctttacc tttgactcta aacagactga 240540
atataatgtg ccattgagaa gactgttttg ccttgtgtgt ttttggggat tactgagtct 240600
gctgtaactg aatgactaaa tctcttgcta gacttgggaa gttttcatct actcattaaa 240660
taggttttct aatccttttgt ctctttgccc ttgaggatac caataatgca aatattcaat 240720
tgctttatgt tgccccaaat attacaaaga ttttgtttat tcttttaaaa ttctttttttc 240780
tttatttttg cataactgga ttatttcaaa agggattctg agataatgag attctttctt 240840
ctgcctgatc tagtatactg ttgaagcttt caaatgtatt gcgagctttt gtatttcctt 240900
caatgaattt ttcccttcca gaatttctat ttggttattt taaaaaatgt atttttggt 240960
taaatttctc attcatatcc tgaattcttt tctgattttt ttttgtattg tttttcagaa 241020
ttctcttgta tctcactgag cttctttaaa tcaatgttta aaattcttta tctggaattt 241080
caaaaatttc tttttgatta aaatctattg ctagagaatt attgtgttcc tctggaggtg 241140
tcatattttc ttgctttttc atgtttcctg ggtccttatg ttgctatctg atgtgatggt 241200
tggtgtaaca gttgtttctt ctcatttttg aatttacttt tgcaggggag gacttttttct 241260
gaagttgcat ctatggagtt gcttgggtag gatacgttgg ctttgattct gagtgcatgc 241320
tgtagtgtag tctctgtatg atttatttga ctgtaaacag catagtagta tctgtgcttt 241380
ccttagtgag ttagggtgtg gttattactg aaggctgtgg tgaagttgtg ttgggggact 241440
agcatgccgt gtgtgccaat attcaggccc caatggtggc agctgtgggc tgaatatgcc 241500
tatattttag ccccaaggtg gtgtacaatg gtgcctgtgt tcatggttac tggtgggcca 241560
attcttaggc ttccaaatgg cttgcttaga ttccagtagt ggcagcgatg gaccaggtga 241620
gtgggtgggt tctcaggcac cttggacagc tgacatggca taggtgatag cagtagcaga 241680
ggtaaggtga ttctctgggt cacaggcagt atgcattgat gttggtggtg gctccaatgg 241740

actgggcagg ccagtctcca ggcctgcatg tggactttgc tggttagcac cagctgaggt 241800
ggtag 241805

<210> 5
<211> 201
<212> DNA
<213> Homo sapiens

<400> 5

caatgtccga attcgaaaat ataatctctc atctgagagg ttctcagagt atcttcaaga 60
tgaggaatat atccaagctg ttgattatga ttgggatccc raggacatag gcctcagtga 120
gtataaactt tggcatcttt cattgatatt aagtgacttt atagaatttt aaggtgttga 180
cttttaagga atttattgtt t 201

<210> 6
<211> 17
<212> DNA
<213> Homo sapiens

<400> 6
ctgaggccta tgtcctc 17

<210> 7
<211> 17
<212> DNA
<213> Homo sapiens

<400> 7
ctgaggccta tgtcctt 17

<210> 8
<211> 21
<212> DNA
<213> Homo sapiens

<400> 8
agctctcctt tgttgctact g 21

Claims

1. A method for determining whether a human has an increased risk for recurrent myocardial infarction (MI), comprising:

   a) testing nucleic acid from said human for the presence or absence of a polymorphism in gene *LRP2* at position 101 ofSEQ ID NO:5 or its complement; and
   b) correlating the presence of G at position 101 of SEQ ID NO:5 or C at position 101 of its complement with said human having said increased risk for recurrent MI, or the absence of said G or said C with said human having no said increased risk for recurrent MI.

2. The method of claim 1 in which said testing is carried out by a process selected from the group consisting of: allele-specific probe hybridization, allele-specific primer extension, allele-specific amplification, sequencing, 5' nuclease digestion, molecular beacon assay, oligonucleotide ligation assay, size analysis, single-stranded conformation polymorphism analysis, and denaturing gradient gel electrophoresis (DGGE).

3. The method of claim 1, wherein said correlating is performed by computer software.

4. The method of claim 1, wherein said nucleic acid has been isolated from cells of a biological sample from said human.

5. The method of claim 4, wherein said biological sample is blood, saliva, or buccal swabs.

6. The method of claim 4, further comprising isolating said nucleic acid from said biological sample prior to said testing step.

7. The method of claim 1, wherein said testing step comprises nucleic acid amplification.

8. The method of claim 7, wherein said nucleic acid amplification is carried out by polymerase chain reaction.

9. The method of claim 1, wherein said method detects said G or said C.

10. The method of claim 1, wherein said human is homozygous or heterozygous for said G or said C.

11. The method of claim 1, wherein said testing step is carried out using a polynucleotide comprising the nucleotide sequence of SEQ ID NO: 6, 7 or 8.

12. Use of an isolated nucleic acid molecule comprising at least 8 contiguous nucleotides of SEQ ID NO: 5, wherein said at least 8 contiguous nucleotides of SEQ ID NO: 5 include position 101 ofSEQ ID NO: 5, or the complement thereof, in the method according to any one of claims 1-11.

13. Use of an amplified polynucleotide containing the single nucleotide polymorphism (SNP) at position 101 of SEQ ID NO:5, or the complement thereof, in the method according to any one of claims 1-11, wherein the amplified polynucleotide is between about 16 and about 1,000 nucleotides in length.

14. Use of claim 13 in which the amplified polynucleotide comprises the nucleotide sequence of SEQ ID NO:5.

15. Use of an isolated polynucleotide which specifically hybridizes to a nucleic acid molecule containing the single nucleotide polymorphism (SNP) at position 101 of SEQ ID NO:5, or the complement thereof, in the method according to any one of claims 1-11.

16. Use of claim 15, wherein the isolated polynucleotide comprises the nucleotide sequence of SEQ ID NO:6 or 7.

17. Use of a test kit comprising a container containing a SNP detection reagent which detects the presence of G or A at position 101 of SEQ ID NO:5 or C or T at position 101 of its complement in the method according to any one of claims 1-11.

Patentansprüche

1. Verfahren zur Bestimmung, ob ein Mensch ein erhöhtes Risiko für einen rezidivierenden Myokardinfarkt (MI) besitzt, umfassend:

   (a) das Testen von Nukleinsäure des Menschen auf das Vorliegen oder Nichtvorhandensein eines Polymorphismus in Gen LRP2 an Position 101 von SEQ ID NO:5 oder ihrer komplementären Sequenz; und
   (b) das Korrelieren des Vorliegens von G an Position 101 von SEQ ID NO:5 oder von C an Position 101 ihrer komplementären Sequenz mit dem Menschen, der das erhöhte Risiko für einen rezidivierenden MI besitzt, oder das Korrelieren des Nichtvorliegens von dem G oder dem C mit dem Menschen, der das erhöhte Risiko für einen rezidivierenden MI nicht besitzt.

2. Verfahren nach Anspruch 1, bei dem das Testen durch ein Verfahren durchgeführt wird, das aus der Gruppe bestehend aus Allel-spezifischer Sondenhybridisierung, Allel-spezifischer Primerextension, Allel-spezifischer Amplifikation, Sequenzierung, 5'-Nuclease-Verdau, Molecular-Beacon-Assay, Oligonukleotid-Ligationsassay, Größenanalyse, Einzelstrang-Konformationspolymorphismusanalyse und denaturierender Gradientengelelektrophorese (DGGE) ausgewählt ist.

3. Verfahren nach Anspruch 1, bei dem das Korrelieren von einer Computersoftware durchgeführt wird.

4. Verfahren nach Anspruch 1, bei dem man die Nukleinsäure aus den Zellen einer biologischen Probe des Menschen isoliert.

5. Verfahren nach Anspruch 4, bei dem die biologische Probe Blut, Speichel oder Wangenabstriche ist.

6. Verfahren nach Anspruch 4, ferner umfassend das Isolieren der Nukleinsäure aus der biologischen Probe vor dem Testschritt.

7. Verfahren nach Anspruch 1, bei dem der Testschritt Nukleinsäureamplifikation umfasst.

8. Verfahren nach Anspruch 7, bei dem man die Nukleinsäureamplifikation durch Polymerase-Kettenreaktion durchführt.

9. Verfahren nach Anspruch 1, bei dem das Verfahren das G oder das C detektiert.

10. Verfahren nach Anspruch 1, bei dem der Mensch homozygot oder heterozygot für das G oder das C ist.

11. Verfahren nach Anspruch 1, bei dem man den Testschritt unter Verwendung eines Polynukleotids durchführt, das die Nukleotidsequenz von SEQ ID NO: 6, 7 oder 8 umfasst.

12. Verwendung eines isolierten Nukleinsäuremoleküls, das mindestens 8 kontinuierliche Nukleotide von SEQ ID NO: 5 umfasst, wobei die mindestens 8 kontinuierlichen Nukleotide von SEQ ID NO: 5 die Position 101 von SEQ ID NO: 5 einschließen, oder der komplementären Sequenz davon, in dem Verfahren nach irgend einem der Ansprüche 1-11.

13. Verwendung eines amplifizierten Polynukleotids, das den Einzelnukleotidpolymorphismus (SNP) an Position 101 von SEQ ID NO: 5 enthält, oder der komplementären Sequenz davon, in dem Verfahren nach irgend einem der Ansprüche 1-11, bei der das amplifizierte Polynukleotid zwischen etwa 16 und etwa 1.000 Nukleotiden lang ist.

14. Verwendung nach Anspruch 13, bei der das amplifizierte Polynukleotid die Nukleotidsequenz von SEQ ID NO: 5 umfasst.

15. Verwendung eines isolierten Polynukleotids, das spezifisch mit einem Nukleinsäuremolekül hybridisiert, das einen Einzelnukleotidpolymorphismus (SNP) an Position 101 von SEQ ID NO: 5 enthält, oder der komplementären Sequenz davon, in dem Verfahren nach irgend einem der Ansprüche 1-11.

16. Verwendung nach Anspruch 15, bei der das isolierte Polynukleotid die Nukleotidsequenz von SEQ ID NO: 6 oder 7 umfasst.

17. Verwendung eines Test-Kits, umfassend einen Behälter, der ein SNP Detektionsreagenz enthält, das das Vorliegen von G oder A an Position 101 von SEQ ID NO:5 oder von C oder T an Position 101 seiner komplementären Sequenz detektiert, in dem Verfahren nach irgend einem der Ansprüche 1-11.

Revendications

1. Procédé destiné à déterminer si un humain a un risque accru d'infarctus du myocarde (MI) récurrent, comprenant les étapes consistant à :

   a) tester l'acide nucléique provenant dudit humain quant à la présence ou à l'absence d'un polymorphisme dans le gène *LRP2* à la position 101 de la SEQ ID NO: 5 ou de son complément ; et
   b) corréler la présence de G à la position 101 de la SEQ ID NO: 5 ou de C à la position 101 de son complément au fait que ledit humain a ledit risque accru de MI récurrent, ou bien l'absence dudit G ou dudit C au fait que ledit humain n'a pas ledit risque accru de MI récurrent.

2. Procédé selon la revendication 1, dans lequel ledit test est effectué au moyen d'une technique choisie dans le groupe constitué par : une hybridation de sonde spécifique d'un allèle, l'extension d'une amorce spécifique d'un allèle, une amplification spécifique d'un allèle, un séquençage, une digestion par une 5'-nucléase, une étude avec balise moléculaire, un test de ligature d'oligonucléotide, une analyse de taille, une analyse d'un polymorphisme de

conformation à simple brin et une électrophorèse sur gel en gradient dénaturant (DGGE).

3. Procédé selon la revendication 1, dans lequel ladite corrélation est effectuée par un logiciel informatique.

4. Procédé selon la revendication 1, dans lequel ledit acide nucléique a été isolé à partir de cellules d'un échantillon biologique provenant dudit humain.

5. Procédé selon la revendication 4, dans lequel ledit échantillon biologique est du sang, de la salive ou des prélèvements buccaux.

6. Procédé selon la revendication 4, comprenant en outre l'isolement dudit acide nucléique à partir dudit échantillon biologique avant ladite étape de test.

7. Procédé selon la revendication 1, dans lequel ladite étape de test comprend une amplification de l'acide nucléique.

8. Procédé selon la revendication 7, dans lequel ladite amplification de l'acide nucléique est effectuée au moyen d'une réaction d'amplification en chaîne par polymérase.

9. Procédé selon la revendication 1, dans lequel ledit procédé détecte ledit G ou ledit C.

10. Procédé selon la revendication 1, dans lequel ledit humain est homozygote ou hétérozygote pour ledit G ou ledit C.

11. Procédé selon la revendication 1, dans lequel ladite étape de test est effectuée en utilisant un polynucléotide comprenant la séquence de nucléotides de la SEQ ID NO: 6, 7 ou 8.

12. Utilisation d'une molécule d'acide nucléique isolé comprenant au moins 8 nucléotides contigus de la SEQ ID NO: 5, dans laquelle lesdits au moins 8 nucléotides contigus de la SEQ ID NO: 5 incluent la position 101 de la SEQ ID NO: 5, ou son complément, dans le procédé selon l'une quelconque des revendications 1 à 11.

13. Utilisation d'un polynucléotide amplifié contenant le polymorphisme d'un seul nucléotide (SNP) à la position 101 de la SEQ ID NO: 5, ou son complément, dans le procédé selon l'une quelconque des revendications 1 à 11, dans laquelle le polynucléotide amplifié a une longueur comprise entre environ 16 et environ 1 000 nucléotides.

14. Utilisation selon la revendication 13, dans laquelle le polynucléotide amplifié comprend la séquence de nucléotides de la SEQ ID NO: 5.

15. Utilisation d'un polynucléotide isolé qui s'hybride spécifiquement à une molécule d'acide nucléique contenant le polymorphisme d'un seul nucléotide (SNP) à la position 101 de la SEQ ID NO: 5, ou de son complément, dans le procédé selon l'une quelconque des revendications 1 à 11.

16. Utilisation selon la revendication 15, dans laquelle le polynucléotide isolé comprend la séquence de nucléotides de la SEQ ID NO: 6 ou 7.

17. Utilisation d'une trousse d'essai comprenant un récipient contenant un réactif de détection de SNP qui détecte la présence de G ou de A à la position 101 de la SEQ ID NO: 5 ou bien de C ou de T à la position 101 de son complément dans le procédé selon l'une quelconque des revendications 1 à 11.

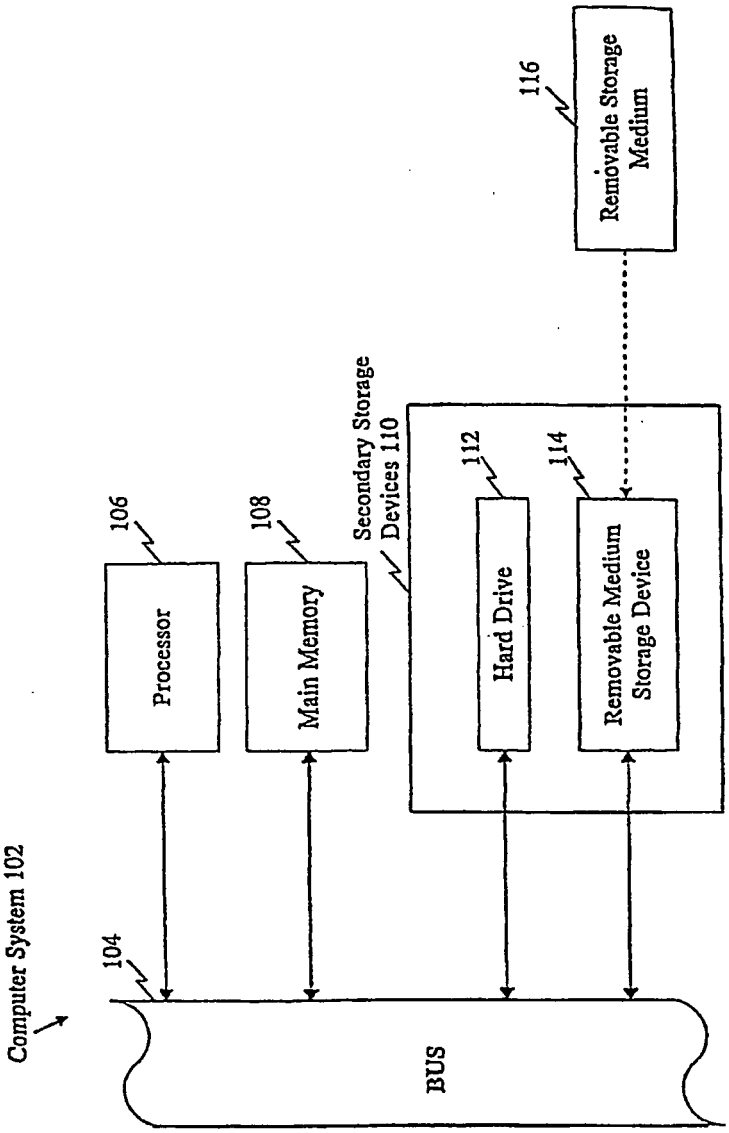
116
Removable Storage Medium
Secondary Storage Devices 110
112
114
106
108
Processor
Main Memory
Hard Drive
Removable Medium Storage Device
Computer System 102
104
BUS

FIGURE 1

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 9740462 A **[0023]**
- WO 0166800 A **[0024]**
- US 4683195 A **[0074]**
- US 4683202 A **[0074]**
- US 5270184 A **[0074]**
- US 5422252 A **[0074]**
- US 5399491 A **[0074]**
- US 6027923 A **[0074]**
- US 5539082 A **[0084]**
- US 5527675 A **[0084]**
- US 5623049 A **[0084]**
- US 5714331 A **[0084]**
- WO 9604000 A **[0085]**
- US 4835263 A **[0086]**
- US 5801115 A **[0086]**
- EP 235726 A, Dattagupta **[0100]**
- WO 8911548 A, Saiki **[0100]**
- US 4988617 A **[0104] [0149]**
- US 4458066 A **[0105]**
- WO 9322456 A **[0107]**
- US 5210015 A **[0110] [0146]**
- US 5538848 A **[0110] [0146]**
- US 5118801 A **[0110] [0148]**
- US 5312728 A **[0110] [0148]**
- US 5866336 A **[0110] [0148]**
- US 6117635 A **[0110] [0148]**
- US 5837832 A, Chee **[0116]**
- WO 9511995 A, Chee **[0116]**
- US 5807522 A, Brown **[0116]**
- US 620332 A **[0121]**
- US 10620333 A **[0121]**
- US 6124478 A **[0121]**
- US 6107024 A **[0121]**
- US 5994073 A **[0121]**
- US 5981768 A **[0121]**
- US 5871938 A **[0121]**
- US 5843681 A **[0121]**
- US 5800999 A **[0121]**
- US 5773628 A **[0121]**
- US 20020110828 A **[0121]**
- WO 95251116 A, Baldeschweiler **[0123]**
- US 5589136 A **[0127]**
- US 6153073 A, Dubrow **[0127]**
- US 6156181 A, Parce **[0127]**
- US 4988167 A **[0144]**
- US 6027889 A **[0150]**
- US 6268148 B **[0150]**
- US 5494810 A **[0150]**
- US 5830711 A **[0150]**
- US 6054564 A **[0150]**
- WO 9731256 A **[0150]**
- WO 0056927 A **[0150]**
- US 0117329 A **[0150]**
- US 09584905 B **[0150]**
- WO 9416101 A **[0155]**
- US 5498531 A **[0157]**
- US 4107288 A **[0220]**
- US 5145684 A **[0220]**
- US 6119096 A **[0239]**
- US 5283317 A **[0288]**
- WO 9410300 A, Brent **[0288]**
- US 4816567 A **[0291]**
- US 4816397 A **[0291]**
- US 5693762 A **[0291]**
- US 5585089 A **[0291]**
- US 5565332 A **[0291]**
- US 4946778 A **[0291]**
- US 5637677 A **[0293]**
- US 4736866 A **[0337]**
- US 4870009 A, Leder **[0337]**
- US 4873191 A, Wagner **[0337]**
- WO 9707668 A **[0339]**
- WO 9707669 A **[0339]**
- EP 03800092 A **[0372]**
- EP 60434778 A **[0372]**
- EP 60453135 A **[0372]**
- EP 60466412 A **[0372]**
- EP 60504955 A **[0372]**

Non-patent literature cited in the description

- **LLOYD-JONES DM.** *Lancet,* 1999, vol. 353, 89-92 **[0006]**
- **WILLIAMS R R.** *Am J Cardiology,* 2001, vol. 87, 129 **[0010]**
- **BROECKEL U.** *Nature Genetics,* 2002, vol. 30, 210 **[0010]**
- **HARRAP S.** *Arterioscler Thromb Vasc Biol,* 2002, vol. 22, 874-878 **[0010]**
- **SHEARMAN A.** *Human Molecular Genetics,* 2000, vol. 9 (9), 1315-1320 **[0010]**
- **GUSELLA.** *Ann. Rev. Biochem.,* 1986, vol. 55, 831-854 **[0014]**

- **WEBER et al.** Human diallelic insertion/deletion polymorphisms. *Am J Hum Genet,* October 2002, vol. 71 (4), 854-62 **[0016]**
- **STEPHENS et al.** *Science,* 20 July 2001, vol. 293, 489-493 **[0018]**
- **LINDER et al.** *Clinical Chemistry,* 1997, vol. 43, 254 **[0023]**
- **MARSHALL.** *Nature Biotechnology,* 1997, vol. 15, 1249 **[0023]**
- **SCHAFER et al.** *Nature Biotechnology,* 1998, vol. 16, 3 **[0023]**
- **YAMADA et al.** Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. *NEW ENGLAND JOURNAL OF MEDICINE,* 12 December 2002, vol. 347 (24), 1916-1923 **[0026]**
- PCR Technology: Principles and Applications for DNA Amplification. Freeman Press, 1992 **[0074]**
- **WU ; WALLACE.** *Genomics,* 1989, vol. 4, 560 **[0074]**
- **LANDEGREN et al.** *Science,* 1988, vol. 241, 1077 **[0074]**
- **GUATELLI et al.** *Proc. Natl. Acad. Sci. USA,* 1990, vol. 87, 1874 **[0074]**
- **SAMBROOK ; RUSSELL.** Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Press, 2000 **[0081] [0084] [0131]**
- **COREY.** Peptide nucleic acids: expanding the scope of nucleic acid recognition. *Trends Biotechnol.,* June 1997, vol. 15 (6), 224-9 **[0084]**
- **HYRUP et al.** Peptide nucleic acids (PNA): synthesis, properties and potential applications. *Bioorg Med Chem.,* January 1996, vol. 4 (1), 5-23 **[0084]**
- **LAGRIFFOUL et al.** *Bioorganic & Medicinal Chemistry Letters,* 1994, vol. 4, 1081-1082 **[0085]**
- **PETERSEN et al.** *Bioorganic & Medicinal Chemistry Letters,* 1996, vol. 6, 793-796 **[0085]**
- **KUMAR et al.** *Organic Letters,* 2001, vol. 3, 1269-1272 **[0085]**
- Current Protocols in Nucleic Acid Chemistry. John Wiley & Sons, 2002 **[0086]**
- Computational Molecular Biology. Oxford University Press, 1988 **[0090]**
- Biocomputing: Informatics and Genome Projects. Academic Press, 1993 **[0090]**
- Computer Analysis of Sequence Data. Humana Press, 1994 **[0090]**
- **HEINJE, G.** Sequence Analysis in Molecular Biology. Academic Press, 1987 **[0090]**
- Sequence Analysis Primer. M Stockton Press, 1991 **[0090]**
- *J. Mol. Biol.,* 1970, 444-453 **[0090]**
- **DEVEREUX, J. et al.** *Nucleic Acids Res.,* 1984, vol. 12 (1), 387 **[0091]**
- **E. MYERS ; W. MILLER.** *CABIOS,* 1989, vol. 4, 11-17 **[0091]**
- **ALTSCHUL et al.** *J. Mol. Biol.,* 1990, vol. 215, 403-10 **[0092]**
- **ALTSCHUL et al.** *Nucleic Acids Res.,* 1997, vol. 25 (17), 3389-3402 **[0092]**
- **PEARSON.** *Methods Mol. Biol.,* 1994, vol. 25, 365-389 **[0092]**
- **DUFRESNE et al.** *Nat Biotechnol,* December 2002, vol. 20 (12), 1269-71 **[0092]**
- Current Protocols in Bioinformatics. John Wiley & Sons, Inc, **[0092]**
- Mutation Detection A Practical Approach. Oxford University Press, 1998 **[0100]**
- **SAIKI et al.** *Nature,* 1986, vol. 324, 163-166 **[0100]**
- **NARANG et al.** *Methods in Enzymology,* 1979, vol. 68, 90 **[0105]**
- **BROWN et al.** *Methods in Enzymology,* 1979, vol. 68, 109 **[0105]**
- **BEAUCAGE et al.** *Tetrahedron Letters,* 1981, vol. 22, 1859 **[0105]**
- **GIBBS.** *Nucleic Acid Res.,* 1989, vol. 17, 2427-2448 **[0107]**
- **LIVAK et al.** *PCR Method Appl.,* 1995, vol. 4, 357-362 **[0110]**
- **TYAGI et al.** *Nature Biotechnology,* 1996, vol. 14, 303-308 **[0110]**
- **NAZARENKO et al.** *Nucl. Acids Res.,* 1997, vol. 25, 2516-2521 **[0110]**
- **LOCKHART, D. J. et al.** *Nat. Biotech.,* 1996, vol. 14, 1675-1680 **[0116]**
- **SCHENA, M. et al.** *Proc. Natl. Acad. Sci.,* 1996, vol. 93, 10614-10619 **[0116]**
- **ZAMMATTEO et al.** New chips for molecular biology and diagnostics. *Biotechnol Annu Rev.,* 2002, vol. 8, 85-101 **[0117]**
- **SOSNOWSLD et al.** Active microelectronic array system for DNA hybridization, genotyping and pharmacogenomic applications. *Psychiatr Genet.,* December 2002, vol. 12 (4), 181-92 **[0117]**
- **HELLER.** DNA microarray technology: devices, systems, and applications. *Annu Rev Biomed Eng.,* 22 March 2002, vol. 4, 129-53 **[0117]**
- **KOLCHINSKY et al.** Analysis of SNPs and other genomic variations using gel-based chips. *Hum Mutat.,* April 2002, vol. 19 (4), 343-60 **[0117]**
- **MCGALL et al.** High-density genechip oligonucleotide probe arrays. *Adv Biochem Eng Biotechnol.,* 2002, vol. 77, 21-42 **[0117]**
- Current Protocols in Molecular Biology. John Wiley & Sons, 1989, 6.3.1-6.3.6 **[0120]**
- **WEIGL et al.** Lab-on-a-chip for drug development. *Adv Drug Deliv Rev.,* 24 February 2003, vol. 55 (3), 349-77 **[0126]**
- **CHEN et al.** Single nucleotide polymorphism genotyping: biochemistry, protocol, cost and throughput. *Pharmacogenomics J.,* 2003, vol. 3 (2), 77-96 **[0144]**
- **KWOK et al.** Detection of single nucleotide polymorphisms. *Curr Issues Mol Biol.,* April 2003, vol. 5 (2), 43-60 **[0144]**
- **SHI.** Technologies for individual genotyping: detection of genetic polymorphisms in drug targets and disease genes. *Am J Pharmacogenomics,* 2002, vol. 2 (3), 197-205 **[0144]**

- **KWOK.** Methods for genotyping single nucleotide polymorphisms. *Annu Rev Genomics Hum Genet,* 2001, vol. 2, 235-58 **[0144]**
- **MAMELLOS.** High-throughput SNP analysis for genetic association studies. *Curr Opin Drug Discov Devel.,* May 2003, vol. 6 (3), 317-21 **[0144]**
- **MYERS et al.** *Science,* 1985, vol. 230, 1242 **[0145]**
- **COTTON et al.** *PNAS,* 1988, vol. 85, 4397 **[0145]**
- **SALEEBA et al.** *Meth. Enzymol.,* 1992, vol. 217, 286-295 **[0145]**
- **ORITA et al.** *PNAS,* 1989, vol. 86, 2766 **[0145]**
- **COTTON et al.** *Mutat. Res.,* 1993, vol. 285, 125-144 **[0145]**
- **HAYASHI et al.** *Genet. Anal. Tech. Appl.,* 1992, vol. 9, 73-79 **[0145]**
- **MYERS et al.** *Nature,* 1985, vol. 313, 495 **[0145] [0156]**
- **WISE et al.** A standard protocol for single nucleotide primer extension in the human genome using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom.,* 2003, vol. 17 (11), 1195-202 **[0153]**
- **BOCKER.** SNP and mutation discovery using base-specific cleavage and MALDI-TOF mass spectrometry. *Bioinformatics,* July 2003, vol. 19 (1), I44-I53 **[0154]**
- **STORM et al.** MALDI-TOF mass spectrometry-based SNP genotyping. *Methods Mol Biol.,* 2003, vol. 212, 241-62 **[0154]**
- **JURINKE et al.** The use of MassARRAY technology for high throughput genotyping. *Adv Biochem Eng Biotechnol.,* 2002, vol. 77, 57-74 **[0154]**
- **JURINKE et al.** Automated genotyping using the DNA MassArray technology. *Methods Mol Biol.,* 2002, vol. 187, 179-92 **[0154]**
- *Biotechniques,* 1995, vol. 19, 448 **[0155]**
- **COHEN et al.** *Adv. Chromatogr.,* 1996, vol. 36, 127-162 **[0155]**
- **GRIFFIN et al.** *Appl. Biochem. Biotechnol.,* 1993, vol. 38, 147-159 **[0155]**
- **ORITA et al.** *Proc. Nat. Acad.* **[0156]**
- Principles and Applications for DNA Amplification. PCR Technology. W.H. Freeman and Co, 1992 **[0156]**
- Modem Epidemiology. Lippincott Williams & Wilkins, 1998, 609-622 **[0161]**
- **WEIR B.** *Genetic Data Analysis,* 1990 **[0164]**
- **HOSMER ; LEMESHOW.** Applied Logistic Regression. Wiley, 2000 **[0166]**
- **DALY et al.** *Nature Genetics,* 2001, vol. 29, 232-235 **[0167]**
- **SCHAID et al.** *Am. J. Hum. Genet.,* 2002, vol. 70, 425-434 **[0168]**
- **WESTFALL et al.** Multiple comparisons and multiple tests. SAS Institute, 1999 **[0169]**
- **BENJAMINI ; HOCHBERG.** *Journal of the Royal Statistical Society, Series B,* 1995, vol. 57, 1289-1300 **[0169]**
- **WESTFALL ; YOUNG.** Resampling-based Multiple Testing. Wiley, 1993 **[0169]**
- Modern Epidemiology. Lippincott Williams & Wilkins, 1998, 643-673 **[0170]**
- **EWENS ; SPIELMAN.** *Am. J. Hum. Genet.,* 1995, vol. 62, 450-458 **[0172]**
- **PRITCHARD et al.** *Am. J. Hum. Gen.,* 1999, vol. 65, 220-228 **[0172]**
- **DEVLIN et al.** *Biometrics,* 1999, vol. 55, 997-1004 **[0172]**
- **DEVLIN et al.** *Genet. Epidem.,* 2001, vol. 21, 273-284 **[0172]**
- **BACANU et al.** *Am. J. Hum. Genet.,* 2000, vol. 66, 1933-1944 **[0173]**
- **KEHOE et al.** *Hum. Mol. Genet.,* 1999, vol. 8, 237-245 **[0173]**
- **DRAPER ; SMITH.** Applied Regression Analysis. Wiley, 1998 **[0174]**
- **HASTIE ; TIBSHIRANI ; FRIEDMAN.** The Elements of Statistical Learning. Springer, 2002 **[0174]**
- **WALL et al.** Haplotype blocks and linkage disequilibrium in the human genome. *Nat Rev Genet.,* August 2003, vol. 4 (8), 587-97 **[0182]**
- **GARNER et al.** On selecting markers for association studies: patterns of linkage disequilibrium between two and three diallelic loci. *Genet Epidemiol.,* January 2003, vol. 24 (1), 57-67 **[0182]**
- **ARDLIE et al.** Patterns of linkage disequilibrium in the human genome. *Nat Rev Genet.,* April 2002, vol. 3 (4), 299-309 **[0182]**
- *Nat Rev Genet,* July 2002, vol. 3 (7), 566 **[0182]**
- **REMM et al.** High-density genotyping and linkage disequilibrium in the human genome using chromosome 22 as a model. *Curr Opin Chem Biol.,* February 2002, vol. 6 (1), 24-30 **[0182]**
- **ROSES.** *Nature,* 2000, vol. 405, 857-865 **[0188]**
- **GOULD ROTHBERG.** *Nature Biotechnology,* 2001, vol. 19, 209-211 **[0188]**
- **EICHELBAUM.** *Clip. Exp. Pharmocol. Physiol.,* 1996, vol. 23 (10-11), 983-985 **[0188]**
- **LINDER.** *Clin. Chem.,* 1997, vol. 43 (2), 254-266 **[0188]**
- **PFOST.** *Trends in Biotechnology,* August 2000 **[0191]**
- **ROSE et al.** Pharmacogenetic analysis of clinically relevant genetic polymorphisms. *Methods Mol Med.,* 2003, vol. 85, 225-37 **[0192]**
- **CACABELOS.** Pharmacogenomics for the treatment of dementia. *Ann Med.,* 2002, vol. 34 (5), 357-79 **[0192]**
- **MAIMONE et al.** Pharmacogenomics of neurodegenerative diseases. *Eur J Pharmacol.,* 09 February 2001, vol. 413 (1), 11-29 **[0192]**
- **POIRIER.** Apolipoprotein E: a pharmacogenetic target for the treatment of Alzheimer's disease. *Mol Diagn.,* December 1999, vol. 4 (4), 335-41 **[0192]**

- **SIEST et al.** Pharmacogenomics of drugs affecting the cardiovascular system. *Clin Chem Lab Med.,* April 2003, vol. 41 (4), 590-9 **[0192]**
- **MUKHERJEE et al.** Pharmacogenomics in cardiovascular diseases. *Prog Cardiovasc Dis.,* May 2002, vol. 44 (6), 479-98 **[0192]**
- **MOOSER et al.** Cardiovascular pharmacogenetics in the SNP era. *J Thromb Haemost.,* July 2003, vol. 1 (7), 1398-402 **[0192]**
- **MCLEOD et al.** Cancer pharmacogenomics: SNPs, chips, and the individual patient. *Cancer Invest.,* 2003, vol. 21 (4), 630-40 **[0192]**
- **WATTERS et al.** Cancer pharmacogenomics: current and future applications. *Biochim Biophys Acta,* 17 March 2003, vol. 1603 (2), 99-111 **[0192]**
- Antisense Drug Technology: Principles, Strategies, and Applications. Marcel Dekker, Inc, 2001 **[0194]**
- **THOMPSON.** *Drug Discovery Today,* 2002, vol. 7 (17), 912-917 **[0194] [0198]**
- **LAVERY et al.** Antisense and RNAi: powerful tools in drug target discovery and validation. *Curr Opin Drug Discov Devel.,* July 2003, vol. 6 (4), 561-9 **[0195] [0199]**
- **STEPHENS et al.** Antisense oligonucleotide therapy in cancer. *Curr Opin Mol Ther.,* April 2003, vol. 5 (2), 118-22 **[0195]**
- **KURRECK.** Antisense technologies. Improvement through novel chemical modifications. *Eur J Biochem.,* April 2003, vol. 270 (8), 1628-44 **[0195]**
- **DIAS et al.** Antisense oligonucleotides: basic concepts and mechanisms. *Mol Cancer Ther.,* March 2002, vol. 1 (5), 347-55 **[0195]**
- **CHEN.** Clinical development of antisense oligonucleotides as anti-cancer therapeutics. *Methods Mol Med.,* 2003, vol. 75, 621-36 **[0195]**
- **WANG et al.** Antisense anticancer oligonucleotide therapeutics. *Curr Cancer Drug Targets,* November 2001, vol. 1 (3), 177-96 **[0195]**
- **BENNETT.** Efficiency of antisense oligonucleotide drug discovery. *Antisense Nucleic Acid Drug Dev.,* June 2002, vol. 12 (3), 215-24 **[0195]**
- **AGAMI.** RNAi and related mechanisms and their potential use for therapy. *Curr Opin Chem Biol.,* December 2002, vol. 6 (6), 829-34 **[0199]**
- **SHI.** Mammalian RNAi for the masses. *Trends Genet,* January 2003, vol. 19 (1), 9-12 **[0199]**
- **SHUEY et al.** RNAi: gene-silencing in therapeutic intervention. *Drug Discovery Today,* October 2002, vol. 7 (20), 1040-1046 **[0199]**
- **MCMANUS et al.** *Nat Rev Genet,* October 2002, vol. 3 (10), 737-47 **[0199]**
- **XIA et al.** *Nat Biotechnol,* October 2002, vol. 20 (10), 1006-10 **[0199]**
- **PLASTERK et al.** *Curr Opin Genet Dev,* October 2000, vol. 10 (5), 562-7 **[0199]**
- **BOSHER et al.** *Nat Cell Biol,* February 2000, vol. 2 (2), E31-6 **[0199]**
- **HUNTER.** *Curr Biol,* 17 June 1999, vol. 9 (12), R440-2 **[0199]**
- **KREN et al.** *Proc. Natl. Acad. Sci. USA,* 1999, vol. 96, 10349-10354 **[0200]**
- **JAZWINSKA.** *A Trends Guide to Genetic Variation and Genomic Medicine,* March 2002, S30-S36 **[0211] [0213]**
- **ROTHBERG.** *Nat Biotechnol,* March 2001, vol. 19 (3), 209-11 **[0212]**
- Current Protocols in Toxicology. John Wiley & Sons, Inc, **[0214]**
- Remington's Pharmaceutical Sciences. Mack Publishing Company, 1990 **[0224]**
- Current Protocols in Pharmacology. John Wiley & Sons, Inc, **[0227]**
- **GILL.** An assessment of the utility of single nucleotide polymorphisms (SNPs) for forensic purposes. *Int J Legal Med.,* 2001, vol. 114 (4-5), 204-10 **[0228]**
- **FRUDAKIS et al.** A Classifier for the SNP-Based Inference of Ancestry. *Journal of Forensic Sciences,* 2003, vol. 48 (4), 771-782 **[0231]**
- **KRAWCZAK.** Informativity assessment for biallelic single nucleotide polymorphisms. *Electrophoresis,* June 1999, vol. 20 (8), 1676-81 **[0238]**
- Current Protocols in Human Genetics. John Wiley & Sons, 2002, 14.1-14.7 **[0241]**
- **SAMBROOK ; RUSSELL.** Molecular Cloning: A Laboratory Manual. Cold Spring Harbor Laboratory Press, 2000 **[0247] [0266] [0311] [0312] [0323]**
- **AUSUBEL et al.** *Current Protocols in Molecular Biology,* 1992 **[0252]**
- **TERPE.** Overview of tag protein fusions: from molecular and biochemical fundamentals to commercial systems. *Appl Microbiol Biotechnol,* 07 November 2002, vol. 60 (5), 523-33 **[0253]**
- **GRADDIS et al.** Designing proteins that work using recombinant technologies. *Curr Pharm Biotechnol.,* December 2002, vol. 3 (4), 285-97 **[0253]**
- **NILSSON et al.** Affinity fusion strategies for detection, purification, and immobilization of recombinant proteins. *Protein Expr Purif.,* October 1997, vol. 11 (1), 1-16 **[0253]**
- **BOWIE et al.** *Science,* 1990, vol. 247, 1306-1310 **[0258]**
- **CUNNINGHAM et al.** *Science,* 1989, vol. 244, 1081-1085 **[0260]**
- **SMITH et al.** *J. Mol. Biol.,* 1992, vol. 224, 899-904 **[0260]**
- **DE VOS et al.** *Science,* 1992, vol. 255, 306-312 **[0260]**
- **T.E. CREIGHTON.** Proteins - Structure and Molecular Properties. W. H. Freeman and Company, 1993 **[0263]**
- **WOLD, F.** Posttranslational Covalent Modification of Proteins. Academic Press, 1983, 1-12 **[0263]**
- **SEIFTER et al.** *Meth. Enzymol.,* 1990, vol. 182, 626-646 **[0263]**

- **RATTAN et al.** *Ann. N.Y. Acad. Sci.,* 1992, vol. 663, 48-62 **[0263]**
- Current Protocols in Protein Science. John Wiley & Sons, 2002 **[0265]**
- Methods in Enzymology: Guide to Molecular Cloning Techniques. Academic Press, 1987 **[0266]**
- Current Protocols in Immunology. John Wiley & Sons **[0270]**
- **HAGE.** Immunoassays. *Anal Chem.,* 15 June 1999, vol. 71 (12), 294R-304R **[0270]**
- **LAM et al.** *Nature,* 1991, vol. 354, 82-84 **[0279]**
- **HOUGHTEN et al.** *Nature,* 1991, vol. 354, 84-86 **[0279]**
- **SONGYANG et al.** *Cell,* 1993, vol. 72, 767-778 **[0279]**
- **HODGSON.** *Bio/technology,* 10 September 1992, 973-80 **[0283]**
- **ZERVOS et al.** *Cell,* 1993, vol. 72, 223-232 **[0288]**
- **MADURA et al.** *J. Biol. Chem.,* 1993, vol. 268, 12046-12054 **[0288]**
- **BARTEL et al.** *Biotechniques,* 1993, vol. 14, 920-924 **[0288]**
- **IWABUCHI et al.** *Oncogene,* 1993, vol. 8, 1693-1696 **[0288]**
- **MORRISON et al.** *Proc. Natl. Acad Sci. USA,* 1984, vol. 81, 6851 **[0291]**
- **NEUBERGER et al.** *Nature,* 1984, vol. 312, 604 **[0291]**
- **WARD et al.** *Nature,* 1989, vol. 334, 544 **[0291]**
- **SEGAL et al.** *J. Immunol. Methods,* 2001, vol. 248, 1 **[0291]**
- **CARTER.** *J. Immunol. Methods,* 2001, vol. 248, 7 **[0291]**
- **TODOROVSKA et al.** *J. Immunol. Methods,* 2001, vol. 248, 47 **[0291]**
- **HARLOW.** Antibodies. Cold Spring Harbor Press, 1989 **[0292]**
- **KOHLER ; MILSTEIN.** *Nature,* 1975, vol. 256, 495 **[0293]**
- **HE et al.** *J. Immunol.,* 2002, vol. 169, 595 **[0293]**
- **HOOGENBOOM ; CHAMES.** *Immunol. Today,* 2000, vol. 21, 371 **[0293]**
- **LIU et al.** *J. Mol. Biol.,* 2002, vol. 315, 1063 **[0293]**
- **MORGAN.** Antibody therapy for Alzheimer's disease. *Expert Rev Vaccines,* February 2003, vol. 2 (1), 53-9 **[0296]**
- **ROSS et al.** Anticancer antibodies. *Am J Clin Pathol.,* April 2003, vol. 119 (4), 472-85 **[0296]**
- **GOLDENBERG.** Advancing role of radiolabeled antibodies in the therapy of cancer. *Cancer Immunol Immunother.,* 11 March 2003, vol. 52 (5), 281-96 **[0296]**
- **ROSS et al.** Antibody-based therapeutics in oncology. *Expert Rev Anticancer Ther.,* February 2003, vol. 3 (1), 107-21 **[0296]**
- **CAO et al.** Bispecific antibody conjugates in therapeutics. *Adv Drug Deliv Rev.,* 10 February 2003, vol. 55 (2), 171-97 **[0296]**
- **VON MEHREN et al.** Monoclonal antibody therapy for cancer. *Annu Rev Med.,* 03 December 2001, vol. 54, 343-69 **[0296]**
- **HUDSON et al.** Engineered antibodies. *Nat Med.,* January 2003, vol. 9 (1), 129-34 **[0296]**
- **BREKKE et al.** Therapeutic antibodies for human diseases at the dawn of the twenty-first century. *Nat Rev Drug Discov.,* January 2003, vol. 2 (1), 52-62 **[0296]**
- *Nat Rev Drug Discov.,* March 2003, vol. 2 (3), 240 **[0296]**
- **HOUDEBINE.** Antibody manufacture in transgenic animals and comparisons with other systems. *Curr Opin Biotechnol.,* December 2002, vol. 13 (6), 625-9 **[0296] [0341]**
- **ANDREAKOS et al.** Monoclonal antibodies in immune and inflammatory diseases. *Curr Opin Biotechnol.,* December 2002, vol. 13 (6), 615-20 **[0296]**
- **KELLERMANN et al.** Antibody discovery: the use of transgenic mice to generate human monoclonal antibodies for therapeutics. *Curr Opin Biotechnol.,* December 2002, vol. 13 (6), 593-7 **[0296]**
- **PINI et al.** Phage display and colony filter screening for high-throughput selection of antibody libraries. *Comb Chem High Throughput Screen,* November 2002, vol. 5 (7), 503-10 **[0296]**
- **BATRA et al.** Pharmacokinetics and biodistribution of genetically engineered antibodies. *Curr Opin Biotechnol.,* December 2002, vol. 13 (6), 603-8 **[0296]**
- **TANGRI et al.** Rationally engineered proteins or antibodies with absent or reduced immunogenicity. *Curr Med Chem.,* December 2002, vol. 9 (24), 2191-9 **[0296]**
- **LEONG et al.** *Cytokine,* 2001, vol. 16, 106 **[0303]**
- **SMITH et al.** *Gene,* 1988, vol. 67, 31-40 **[0316]**
- **AMANN et al.** *Gene,* 1988, vol. 69, 301-315 **[0316]**
- **STUDIER et al.** *Gene Expression Technology: Methods in Enzymology,* 1990, vol. 185, 60-89 **[0316]**
- **GOTTESMAN, S.** Gene Expression Technology: Methods in Enzymology. Academic Press, 1990, vol. 185, 119-128 **[0317]**
- **WADA et al.** *Nucleic Acids Res.,* 1992, vol. 20, 2111-2118 **[0317]**
- **BALDARI et al.** *EMBO J.,* 1987, vol. 6, 229-234 **[0318]**
- **KURJAN et al.** *Cell,* 1982, vol. 30, 933-943 **[0318]**
- **SCHULTZ et al.** *Gene,* 1987, vol. 54, 113-123 **[0318]**
- **SMITH et al.** *Mol. Cell Biol.,* vol. 3, 2156-2165 **[0319]**
- **LUCKLOW et al.** *Virology,* 1989, vol. 170, 31-39 **[0319]**
- **SEED, B.** *Nature,* 1987, vol. 329, 840 **[0320]**
- **KAUFMAN et al.** *EMBO J,* 1987, vol. 6, 187-195 **[0320]**
- Current Protocols in Molecular Biology. John Wiley & Sons **[0331]**
- **HOGAN, B.** Manipulating the Mouse Embryo. Cold Spring Harbor Laboratory Press, 1986 **[0337]**
- **LAKSO et al.** *PNAS,* 1992, vol. 89, 6232-6236 **[0338]**

- **O'GORMAN et al.** *Science,* 1991, vol. 251, 1351-1355 **[0338]**
- **WILMUT, I. et al.** *Nature,* 1997, vol. 385, 810-813 **[0339]**
- **PETTERS et al.** Transgenic animals as models for human disease. *Transgenic Res.,* 2000, vol. 9 (4-5), 345-6347-51 **[0341]**
- **WOLF et al.** Use of transgenic animals in understanding molecular mechanisms of toxicity. *J Pharm Pharmacol.,* June 1998, vol. 50 (6), 567-74 **[0341]**
- **ECHELARD.** Recombinant protein production in transgenic animals. *Curr Opin Biotechnol.,* October 1996, vol. 7 (5), 536-40 **[0341]**
- **HOUDEBINE.** Transgenic animal bioreactors. *Transgenic Res.,* 2000, vol. 9 (4-5), 305-20 **[0341]**
- **PIRITY et al.** Embryonic stem cells, creating transgenic animals. *Methods Cell Biol.,* 1998, vol. 57, 279-93 **[0341]**
- **ROBL et al.** Artificial chromosome vectors and expression of complex proteins in transgenic animals. *Theriogenology,* 01 January 2003, vol. 59 (1), 107-13 **[0341]**
- **ALTSCHUL.** *J. Mol. Biol.,* 1990, vol. 215, 403-410 **[0346]**
- **BRUTLAG.** *Comp. Chem.,* 1993, vol. 17, 203-207 **[0346]**
- **GERMER S. ; HOLLAND M.J. ; HIGUCHI R.** *Genome Res.,* 2000, vol. 10, 258-266 **[0357] [0368]**

专利名称(译)	与心肌梗塞相关的遗传多态性，检测方法及其用途		
公开(公告)号	EP1583771A4	公开(公告)日	2010-01-27
申请号	EP2003800092	申请日	2003-12-22
[标]申请(专利权)人(译)	阿普里拉股份有限公司		
申请(专利权)人(译)	Applera公司		
当前申请(专利权)人(译)	Applera公司		
[标]发明人	CARGILL MICHELE DEVLIN JAMES J IAKOUBOVA OLGA		
发明人	CARGILL, MICHELE DEVLIN, JAMES J. IAKOUBOVA, OLGA		
IPC分类号	C12Q1/68 A61B C07H21/00 C07H21/04 C07K14/47 C07K14/705 C07K16/18 C07K16/28 C12N15/12 C12P19/34 G01N33/53		
CPC分类号	A61P9/10 C12Q1/6883 C12Q2600/156		
优先权	60/434778 2002-12-20 US 60/453135 2003-03-10 US 60/466412 2003-04-30 US 60/504955 2003-09-23 US		
其他公开文献	EP1583771B1 EP1583771A2		
外部链接	Espacenet		

摘要(译)

本发明基于与心肌梗塞相关的遗传多态性的发现。特别地，本发明涉及含有多态性的核酸分子，由这种核酸分子编码的变体蛋白，用于检测多态性核酸分子和蛋白质的试剂，以及使用该核酸和蛋白质的方法以及使用方法。用于检测的试剂。

Description of column headings for Table 7:

Table 7 column heading	Definition
Gene	Locus Link HUGO approved gene symbol
Marker	Internal hCV identification number for the tested SNP
Sample Set	Sample Set used in the analysis (CARE, Pre-CARE or WGS_S0012)
p-value	Result of the asymptotic chi square test for allelic association, dominant genotypic association, recessive genotypic association, or the allelic, dominant, or recessive p-value of the stratified analysis
OR	odds ratio
95%CI	95% confidence interval of the given odds ratio
Case_Freq	Allele frequency of minor allele in cases
Control_Freq	Allele frequency of minor allele in controls
Allele1	Nucleotide (allele) of the tested SNP for which statistics are being reported
Mode	The mode of inheritance
Strata	Indicates if the analysis of the dataset was based on a substratum such as gender, age, BMI, Hypertension, Fasting Glucose levels, etc. (strata are described below)