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**Liew**

(54) **METHOD FOR THE DETECTION OF GENE TRANSCRIPTS IN BLOOD AND USES THEREOF**

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(63) Continuation of application No. 10/601,518, filed on Jun. 20, 2003, now abandoned, which is a continuation-in-part of application No. 10/268,730, filed on Oct. 9, 2002, now Pat. No. 7,598,031, which is a continuation of application No. 09/477,148, filed on Jan. 4, 2000, now abandoned.

(60) Provisional application No. 60/115,125, filed on Jan. 6, 1999.

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(52) **U.S. Cl.** ..... **435/6.11**; 435/6.12; 436/501

(57) **ABSTRACT**

The present invention is directed to detection and measurement of gene transcripts ad their equivalent nucleic acid products in blood. Specifically provided is analysis performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen.

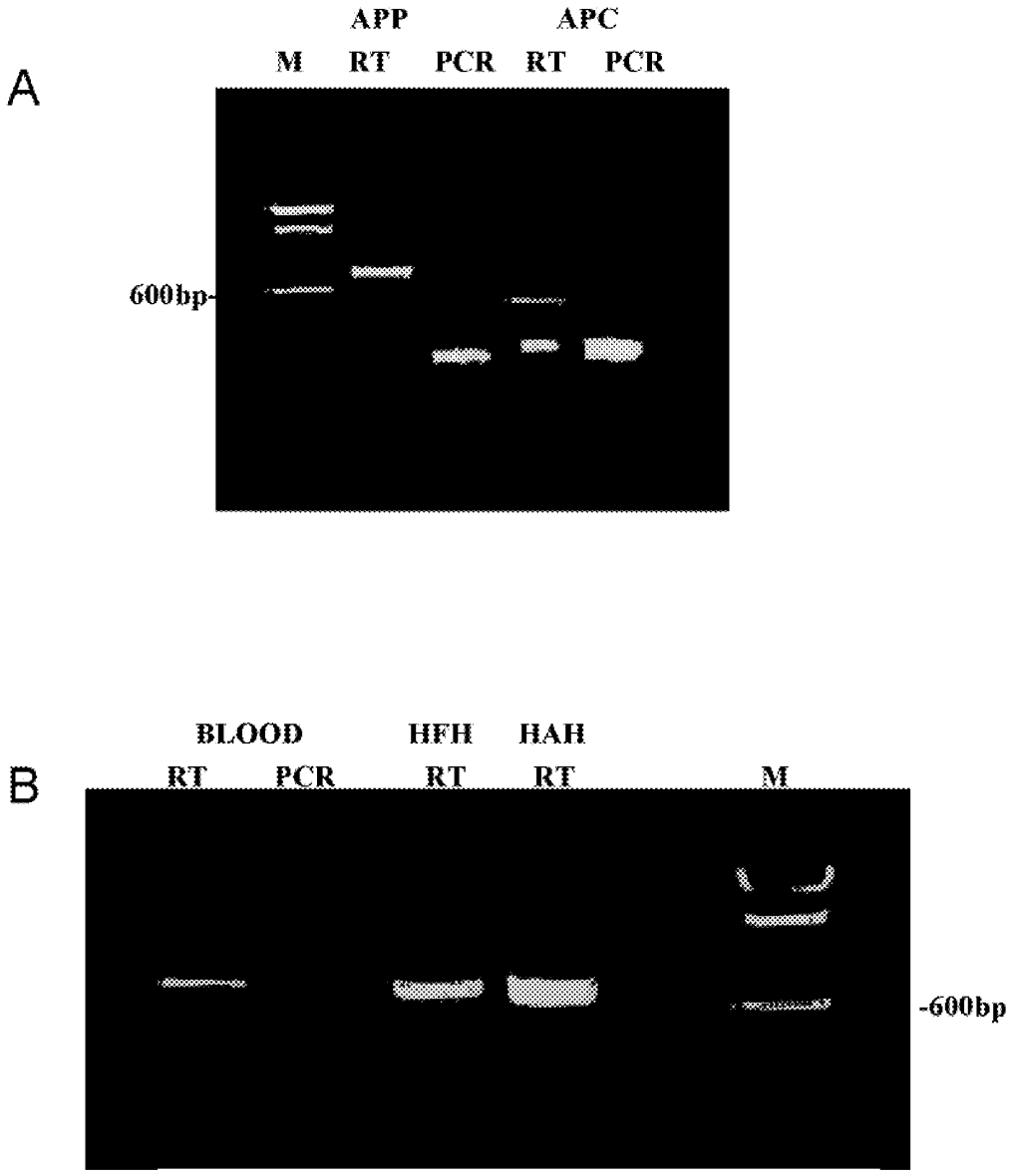

A
APP
APC
M
RT
PCR
RT
PCR
600bp
B
BLOOD
HFH
HAH
RT
PCR
RT
RT
M
-600bp

Figure 1

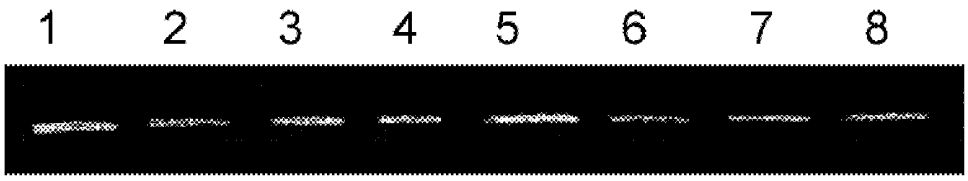



Figure 2

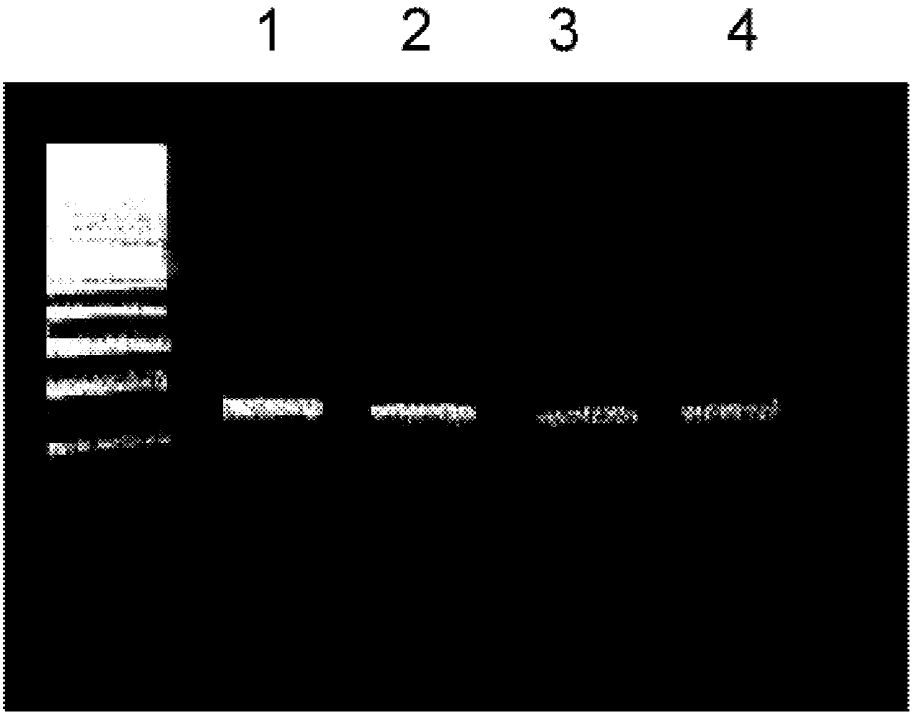



Figure 3

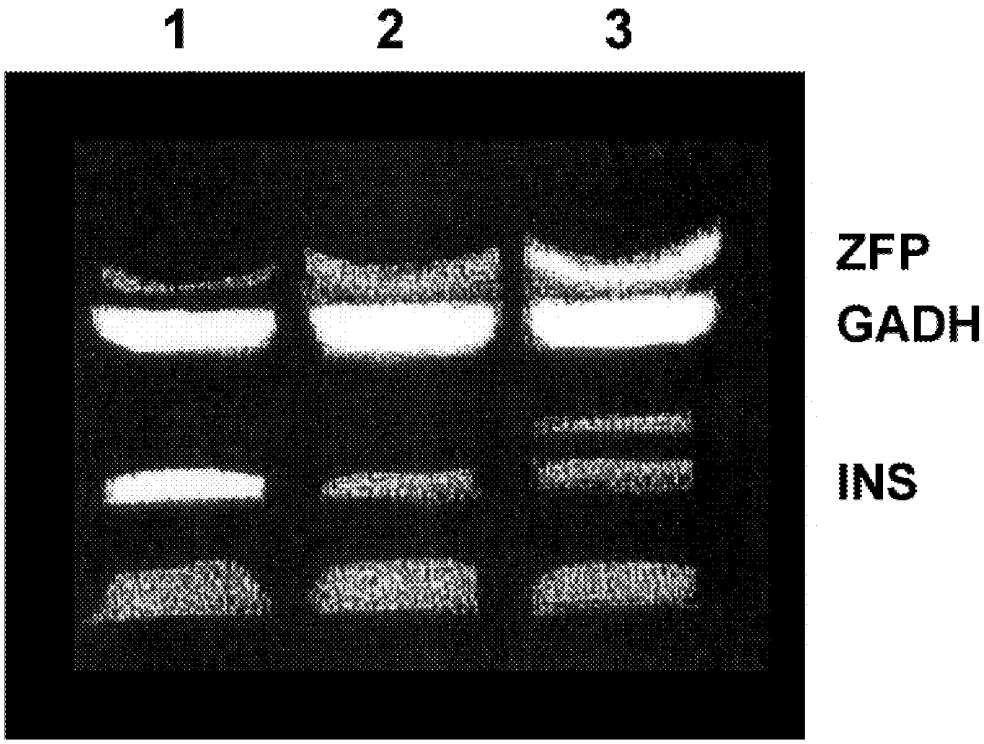



Figure 4

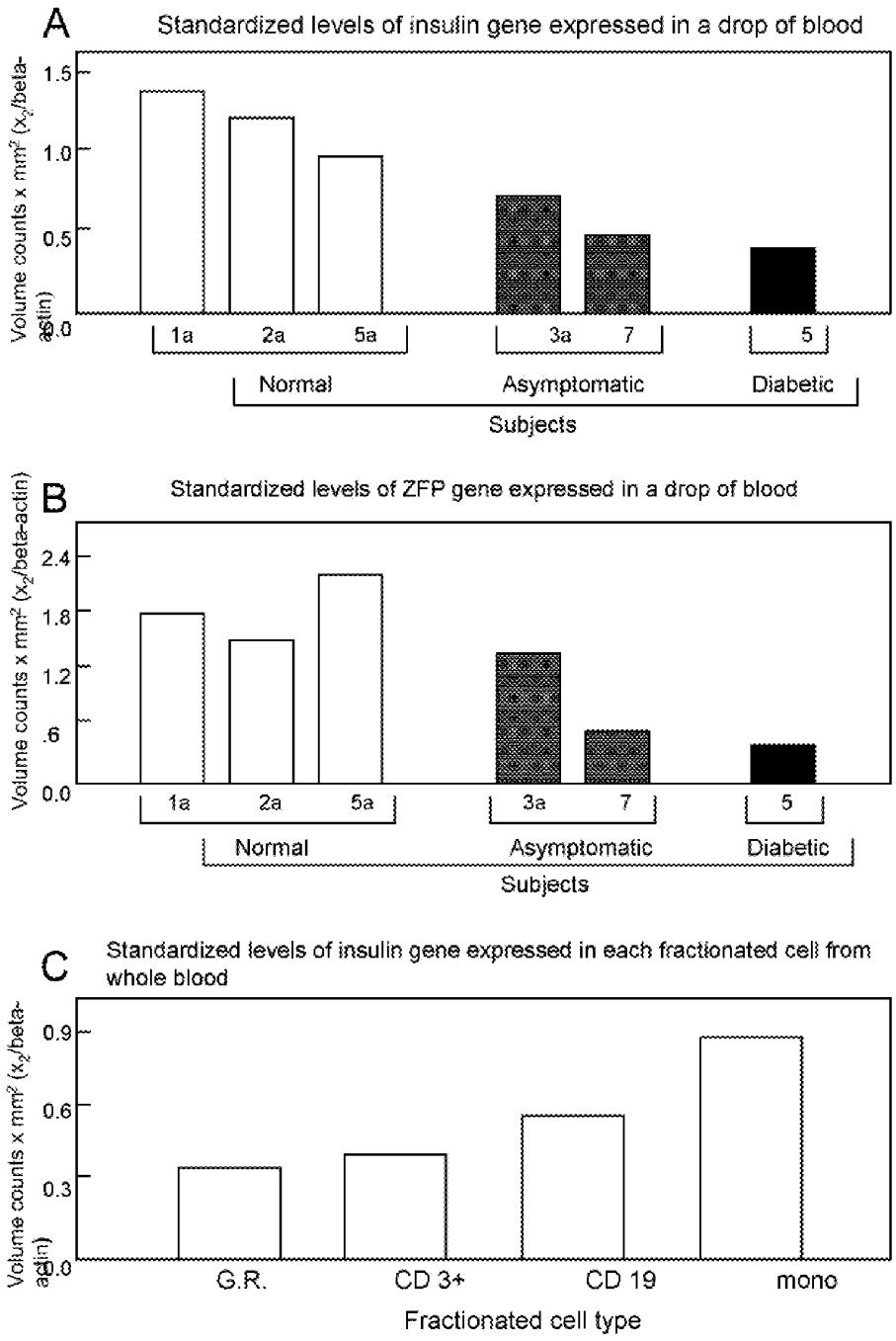

A
Standardized levels of insulin gene expressed in a drop of blood
Volume counts x mm² (x₂/beta-actin)
1.5
1.0
0.5
0.0
1a
2a
5a
3a
7
5
Normal
Asymptomatic
Diabetic
Subjects
B
Standardized levels of ZFP gene expressed in a drop of blood
Volume counts x mm² (x₂/beta-actin)
2.4
1.8
1.2
.6
0.0
1a
2a
5a
3a
7
5
Normal
Asymptomatic
Diabetic
Subjects
C
Standardized levels of insulin gene expressed in each fractionated cell from whole blood
Volume counts x mm² (x₂/beta-actin)
0.9
0.6
0.3
0.0
G.R.
CD 3+
CD 19
mono
Fractionated cell type

Figure 5

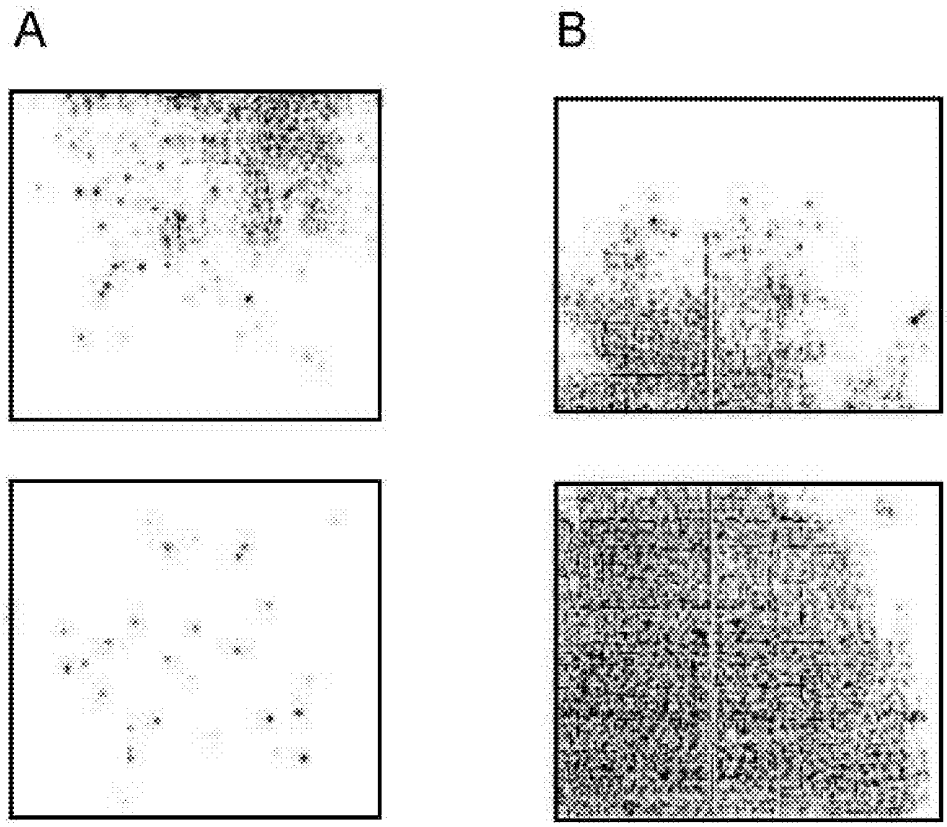



Figure 6

Total: 13,283 ESTs
Known: 6,283
Mitochondrial: 405
Ribosome: 498
Repeat: 868
Mis.: 156
Novel: 2,718

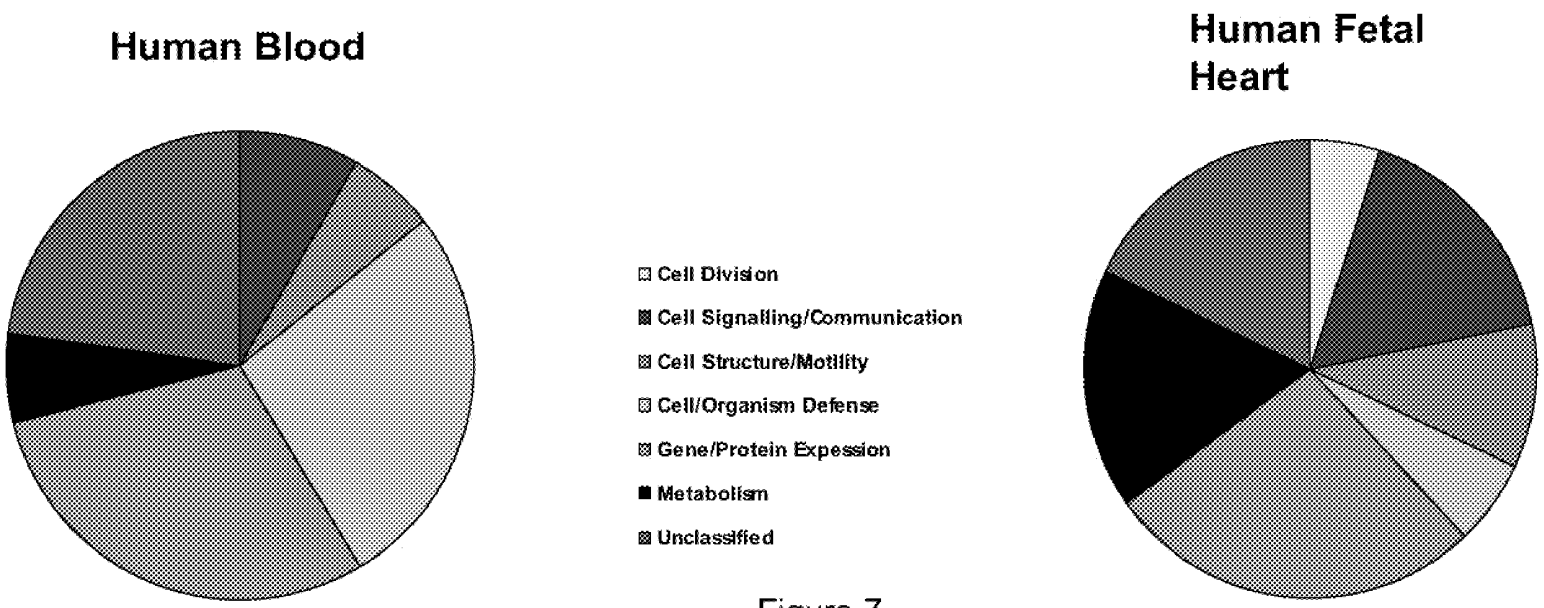
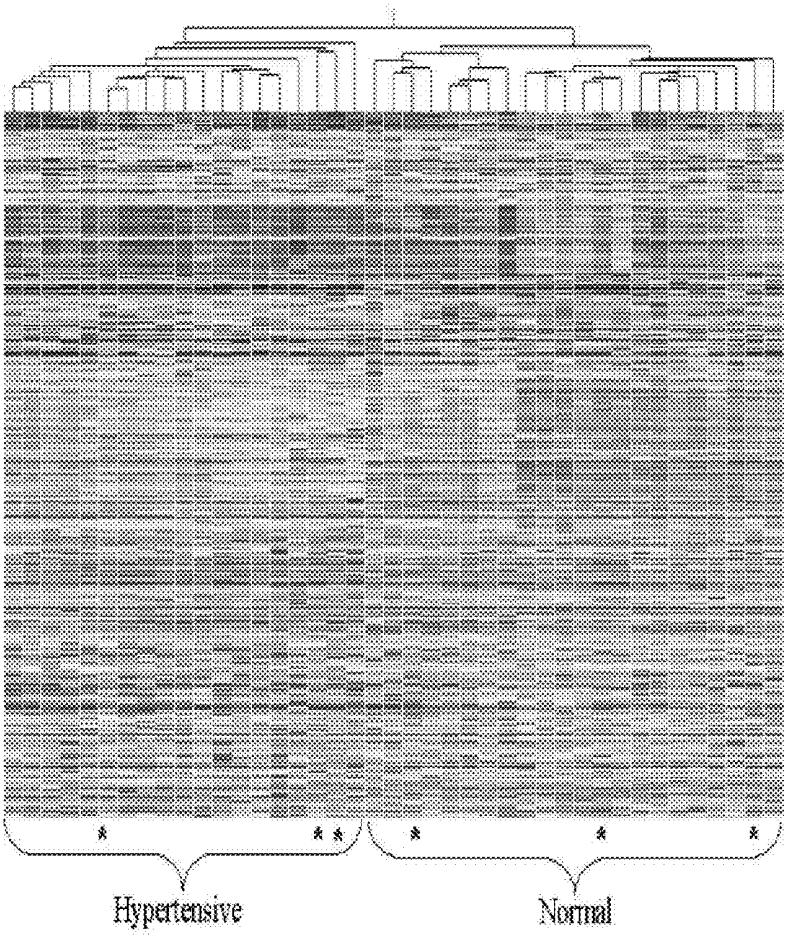



Figure 7

Figure 8

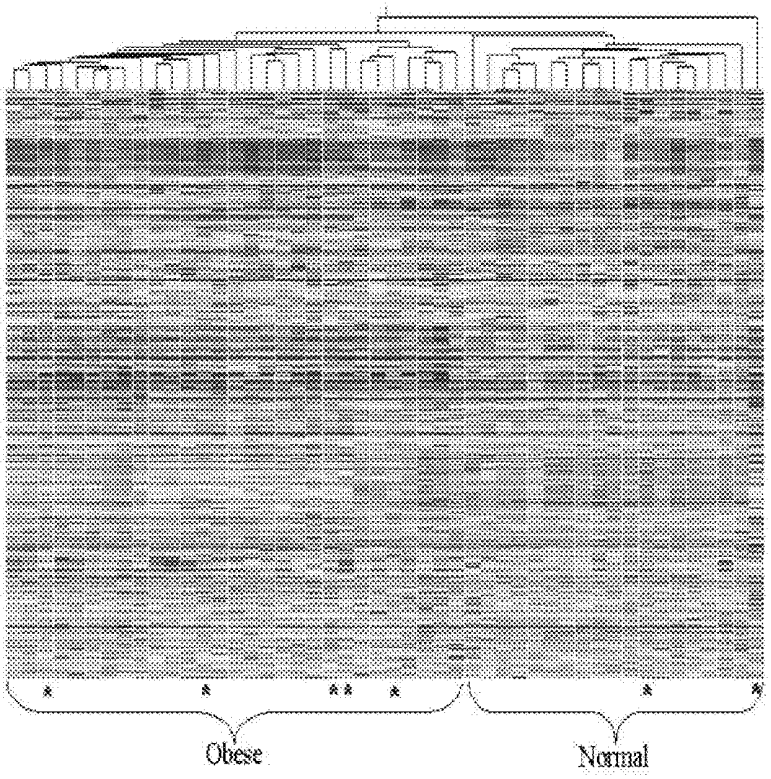
Hypertension




Hypertensive: 19
Normal: 22
Differentially Expressed Genes ($p<0.05$): 861

Figure 9

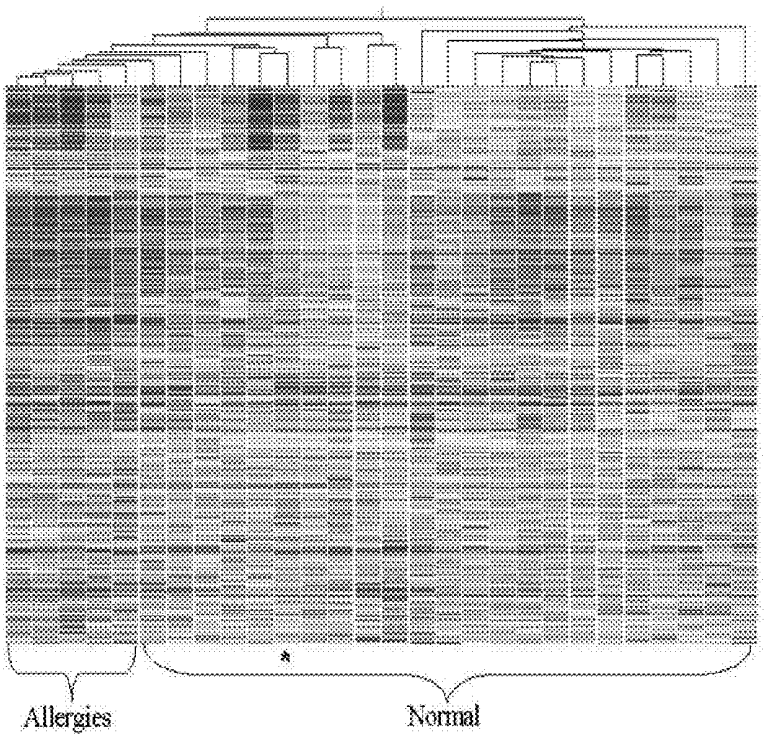
Obesity




Obese: 25
Normal: 22
Differentially Expressed Genes ($p<0.05$): 913

Figure 10

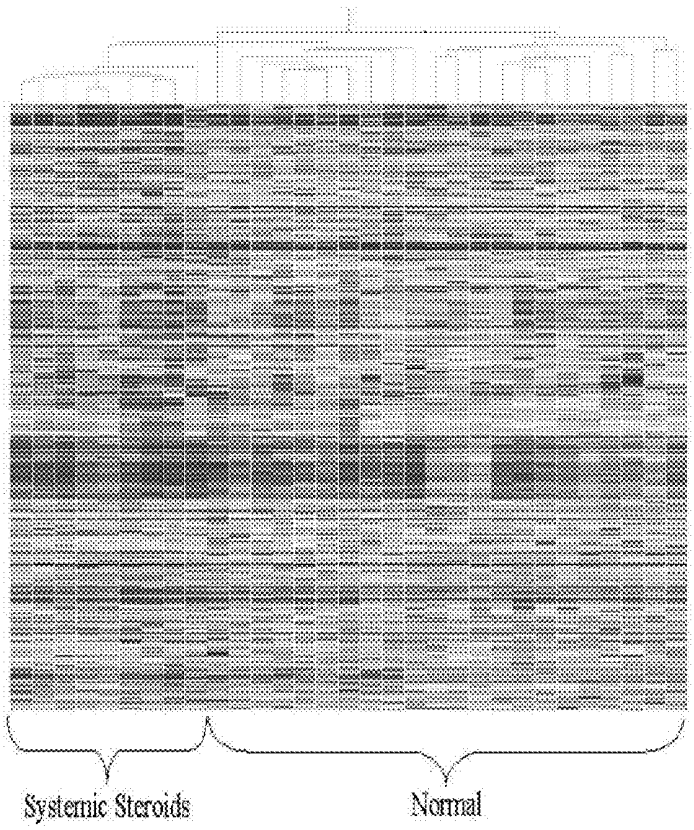
Allergies




Allergies: 6
Normal: 22
Differentially Expressed Genes ($p<0.05$): 633

Figure 11

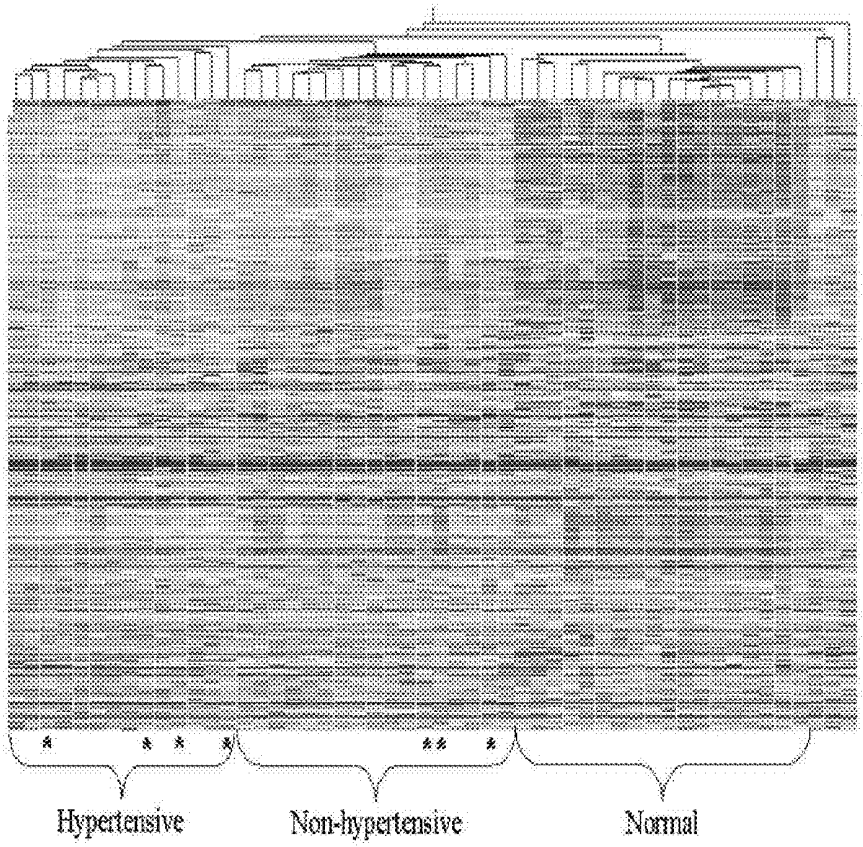
Systemic Steroids




Systemic Steroids: 9
Normal: 22
Differentially Expressed Genes ($p<0.05$): 605

Figure 12

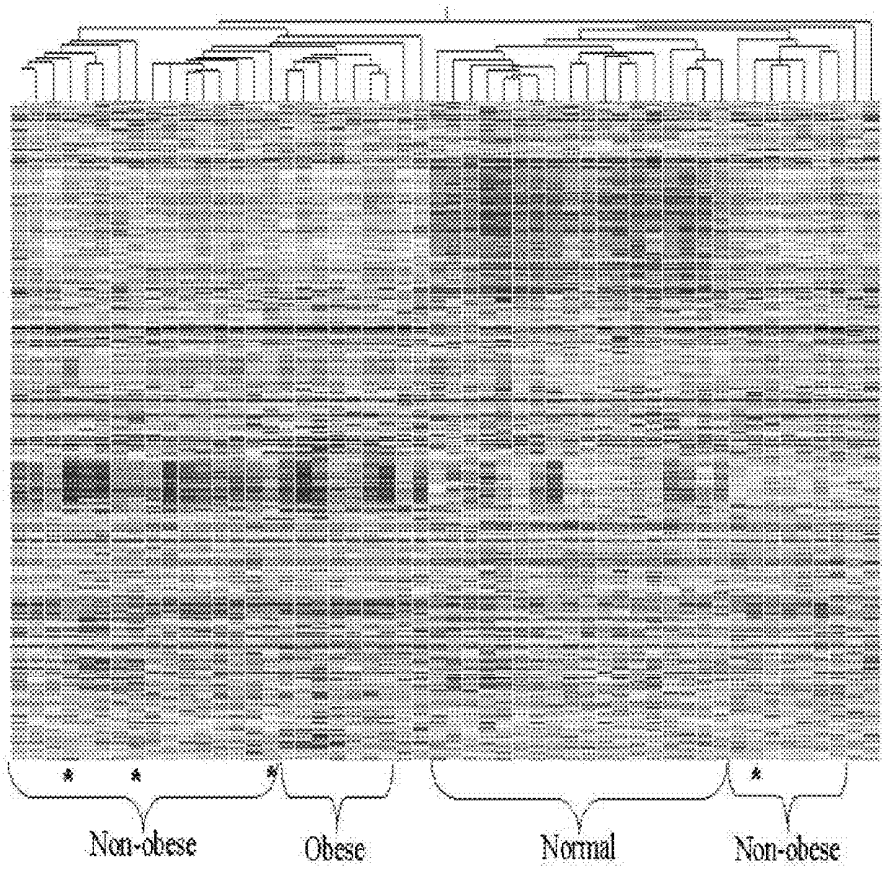
Hypertension




Hypertensive: 10
Non-hypertensive: 18
Normal: 24
Differentially Expressed Genes ($p<0.05$): 1,993

Figure 13

Obesity




Obese: 8
Non-obese: 20
Normal: 24
Differentially Expressed Genes ($p<0.05$): 1,147

Figure 14

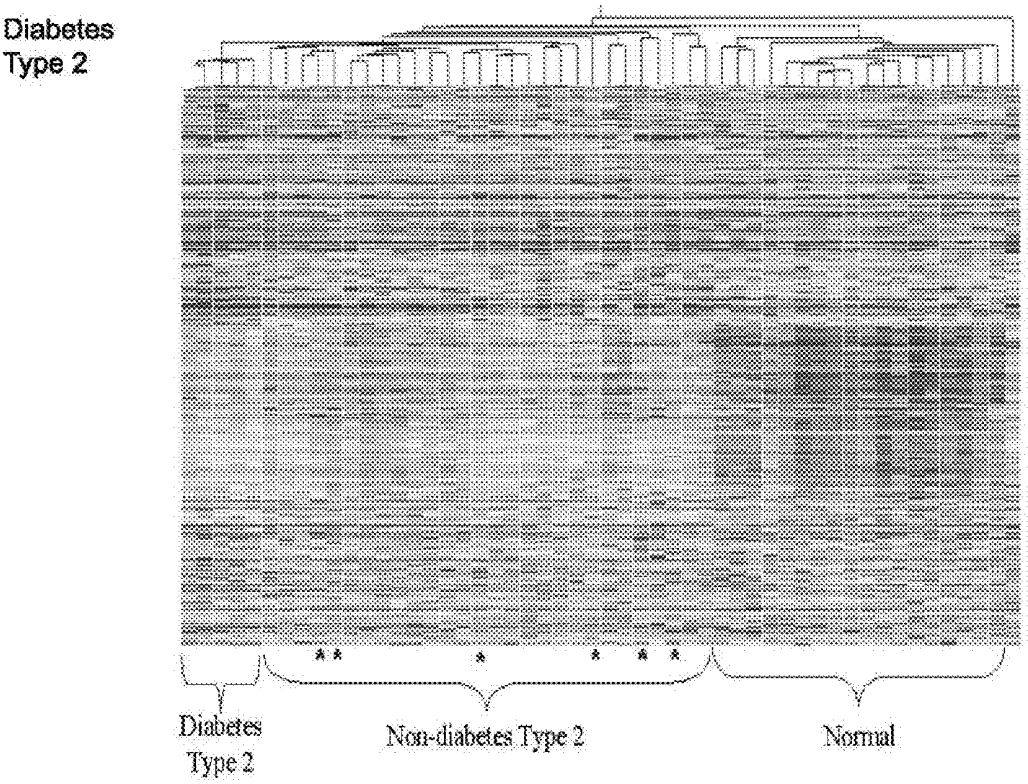
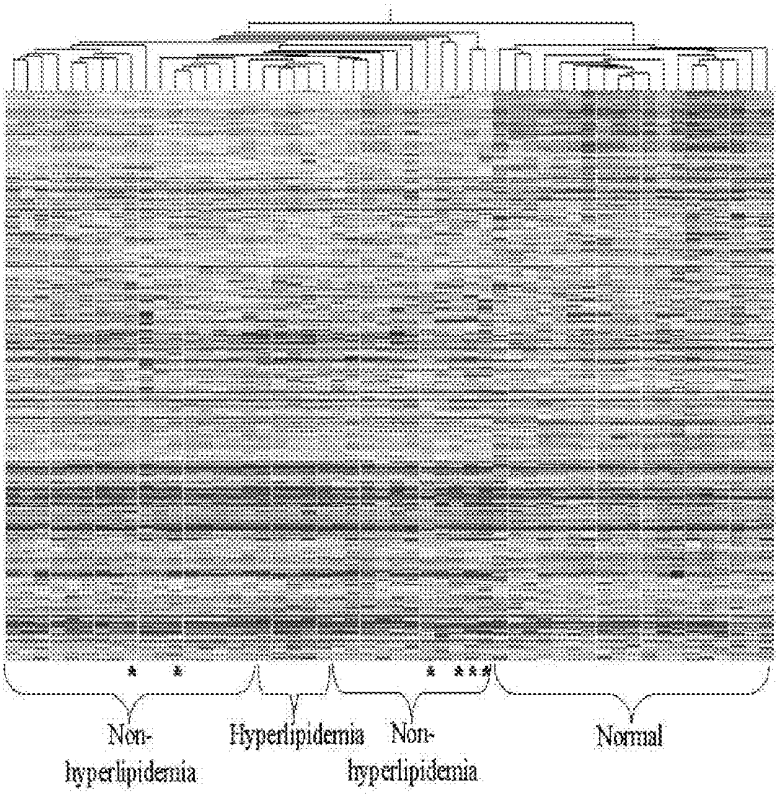

Diabetes Type 2
Diabetes Type 2
Non-diabetes Type 2
Normal
Diabetes Type 2: 5
Non-diabetes Type 2: 23
Normal: 24
Differentially Expressed Genes (p<0.05): 915

Figure 15

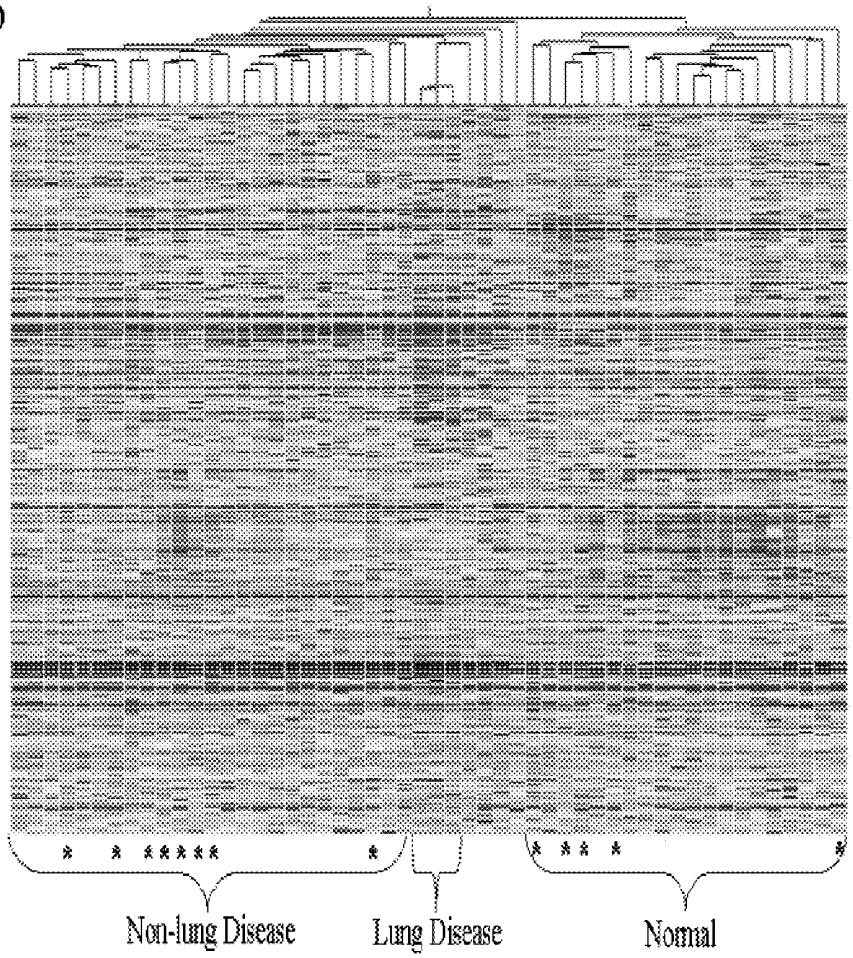
Hyperlipidemia




Hyperlipidemia: 7
Non-hyperlipidemia: 21
Normal: 24
Differentially Expressed Genes ($p<0.05$): 1,022

Figure 16

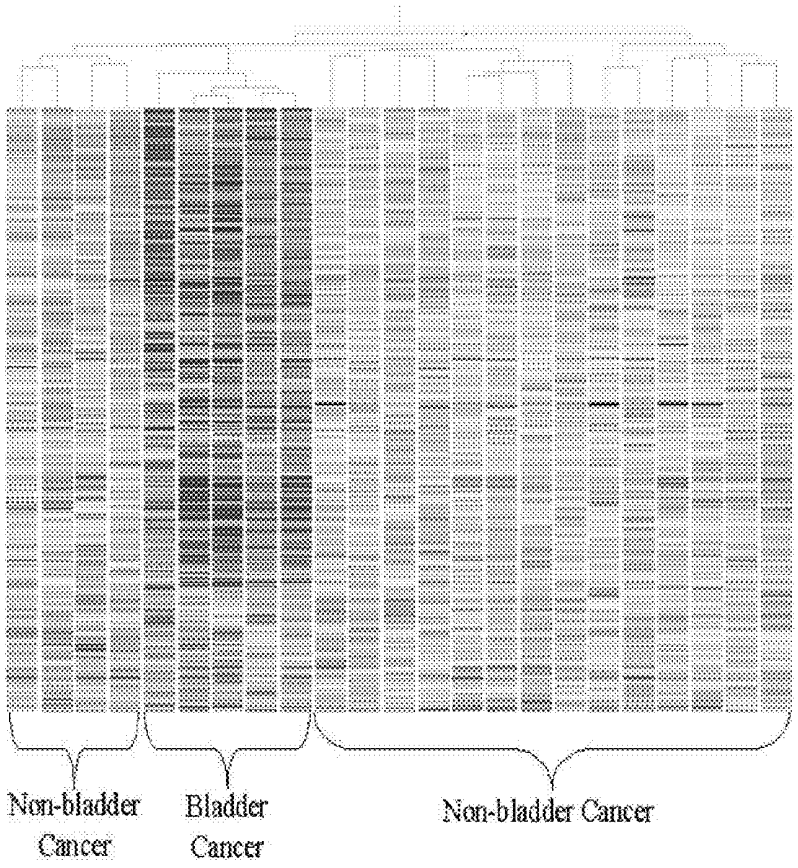
Lung Disease




Lung Disease: 3
Non-lung Disease: 25
Normal: 24
Differentially Expressed Genes ($p<0.05$): 596

Figure 17

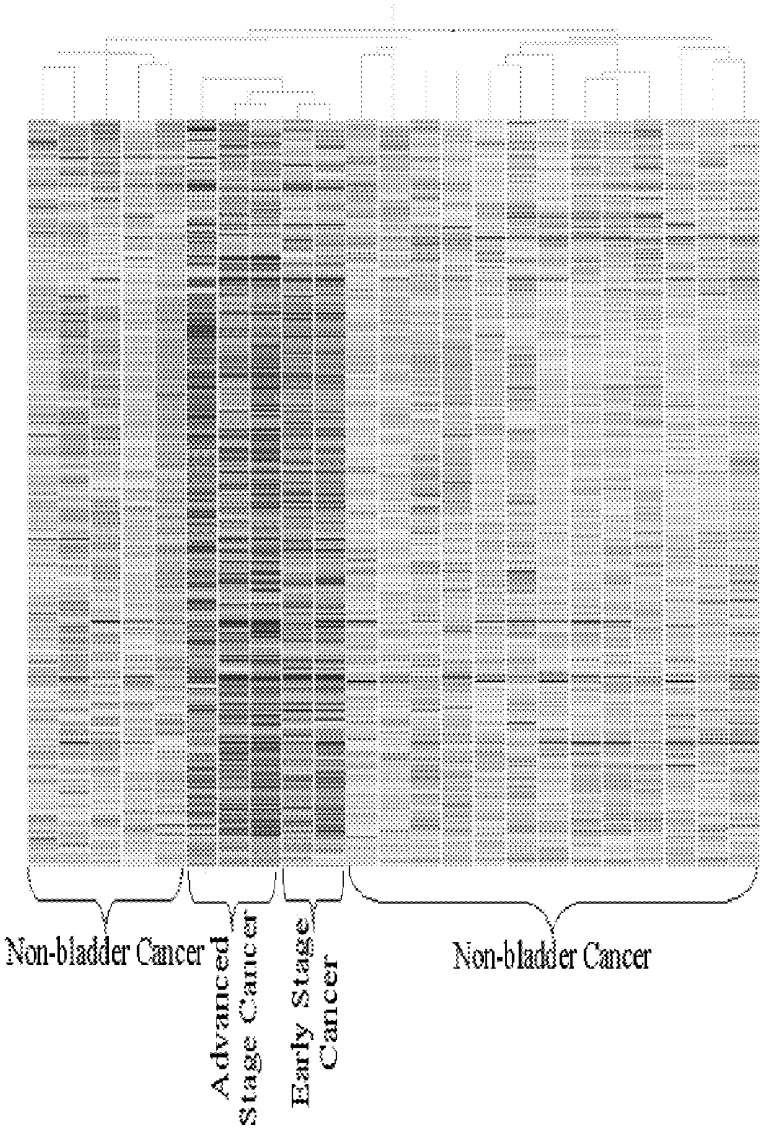
Bladder Cancer




Bladder Cancer: 5
Non-bladder Cancer: 18
Differentially Expressed Genes ($p<0.05$): 4,228

Figure 18

Bladder Cancer



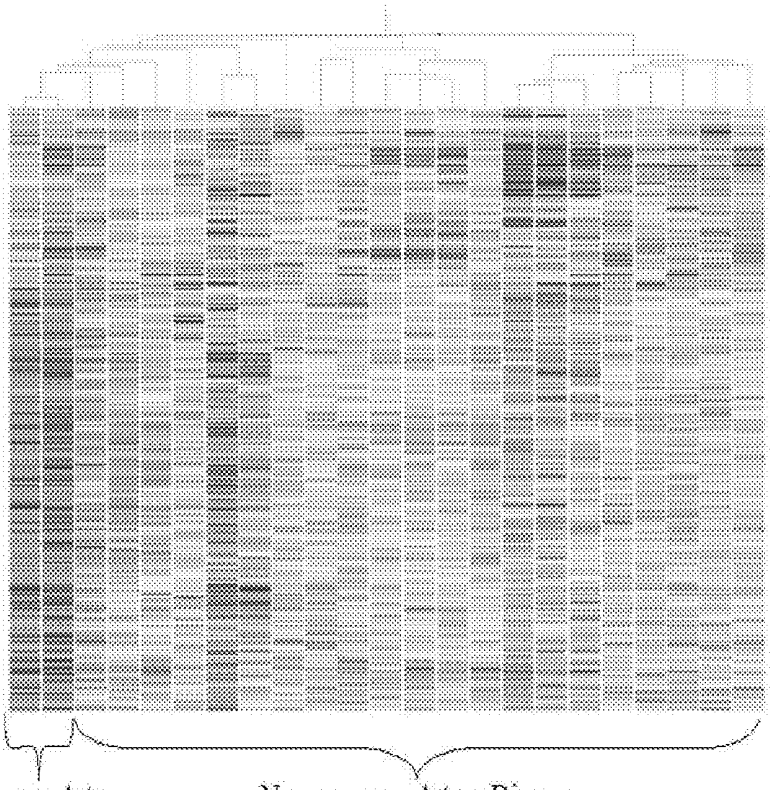

Bladder Cancer: 3 advanced stage, 2 early stage

Non-bladder Cancer: 18

Differentially Expressed Genes ($p<0.05$): 3,518

Figure 19

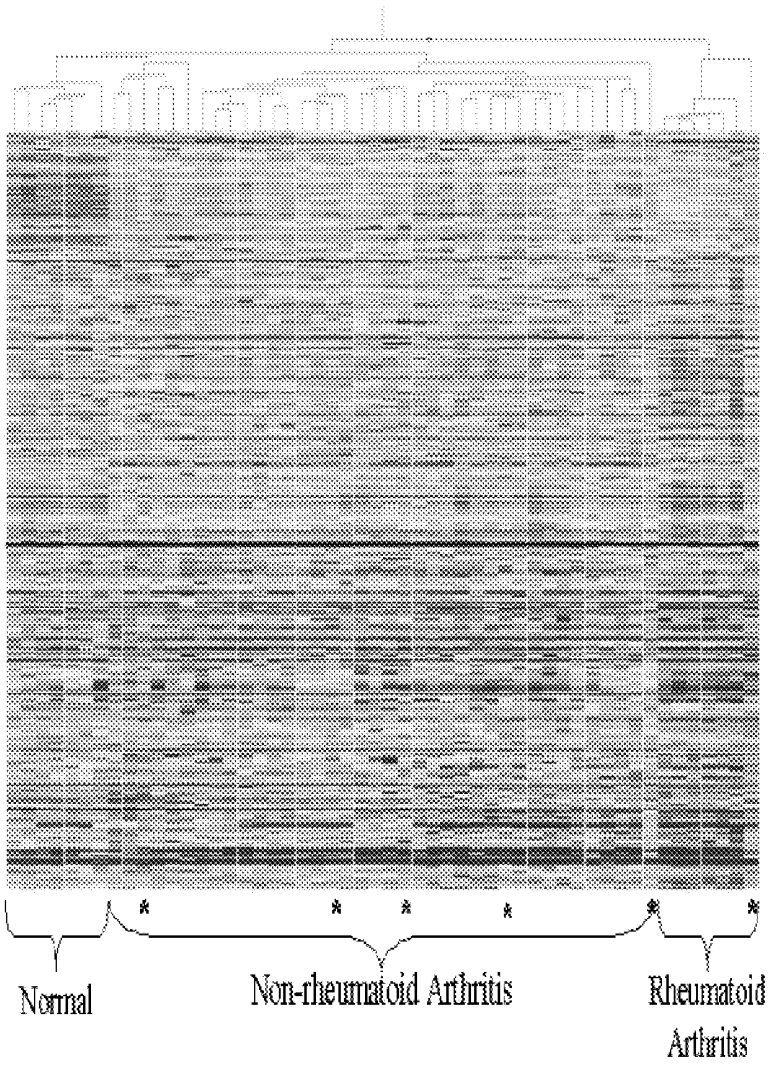
Coronary Artery Disease




Coronary Artery Disease: 2
Non-coronary Artery Disease: 21
Differentially Expressed Genes ($p<0.05$): 967

Figure 20

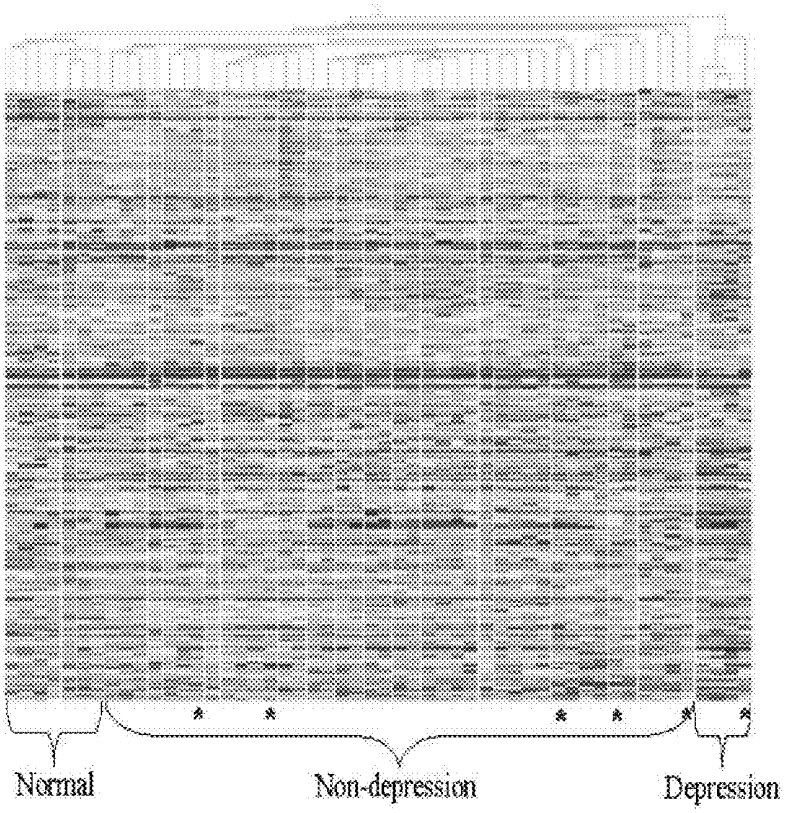
Rheumatoid Arthritis




Rheumatoid Arthritis: 6
Non-rheumatoid Arthritis: 34
Normal: 12
Differentially Expressed Genes ($p<0.05$): 2,068

Figure 21

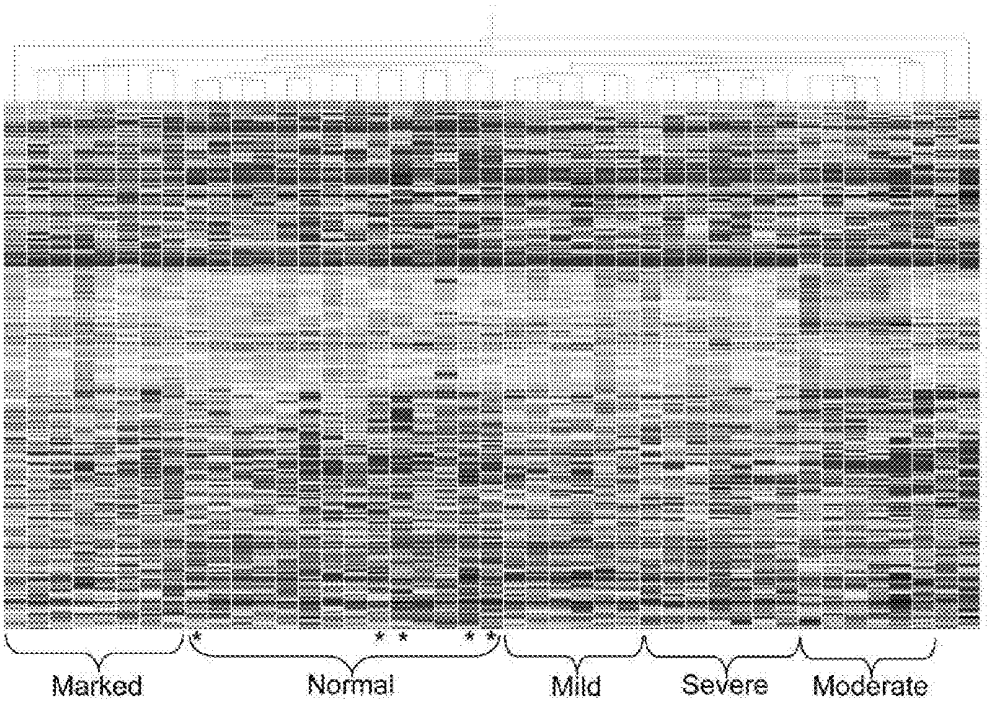
Depression




Depression: 3
Non-depression: 37
Normal: 12
Differentially Expressed Genes ($p<0.05$): 941

Figure 22

Osteoarthritis




Osteoarthritis: 9 mild, 8 moderate, 8 marked, 9 severe
Normal: 9
Differentially Expressed Genes ($p<0.05$): 300

**Figure 23**

RT-PCR of overexpressed genes in CAD peripheral blood cells identified using microarray experiments, including PBP, PF4 and F13A

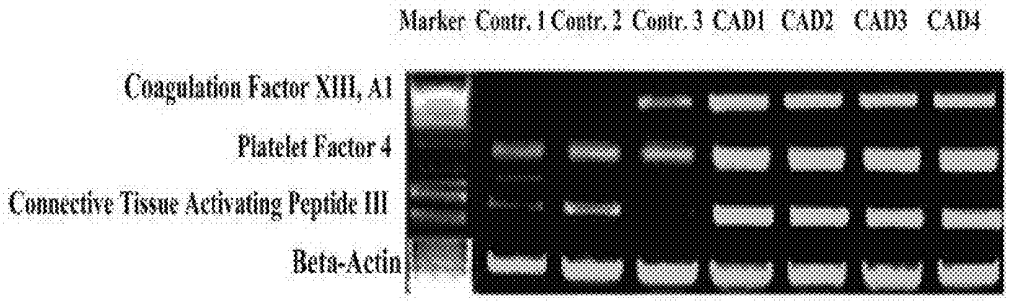
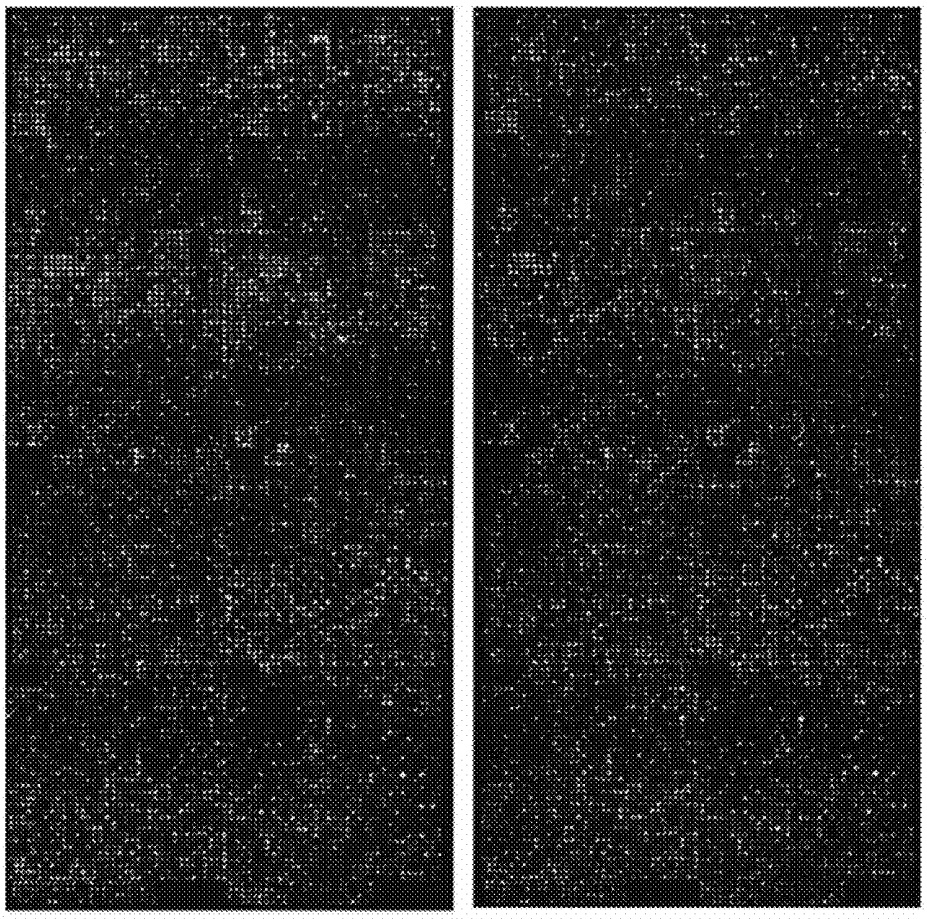


Figure 24



# METHOD FOR THE DETECTION OF GENE TRANSCRIPTS IN BLOOD AND USES THEREOF

## RELATED APPLICATIONS

**[0001]** This application is a continuation of U.S. application Ser. No. 10/601,518, filed on Jun. 20, 2003, which is a continuation-in-part of application Ser. No. 10/268,730, filed on Oct. 9, 2002, now issued as U.S. Pat. No. 7,598,031, which is a continuation of U.S. application Ser. No. 09/477,148, filed Jan. 4, 2000, now abandoned, which claims the benefit of U.S. Provisional Application No. 60/115,125, filed on Jan. 6, 1999, the entirety of which is incorporated herein by reference.

## TABLES

## LENGTHY TABLES

The patent application contains a lengthy table section. A copy of the table is available in electronic form from the USPTO web site (http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20110275069A1). An electronic copy of the table will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

**[0002]** This application includes a compact disc in duplicate (2 compact discs: Tables copy 1 and Tables copy 2), which are hereby incorporated by reference in their entirely. Each compact disc contains the following files (corresponding to Tables 2-4):

| FILE NAMES | SIZE | DATE OF CREATION |
|---|---|---|
| TABLE 2 | 363 KB | Jun. 30, 2010 |
| TABLE 3A (GeneListFigure8.hyperten) | 136 KB | Jun. 30, 2010 |
| TABLE 3B (GeneListFigure9.obesity) | 144 KB | Jun. 30, 2010 |
| TABLE 3C (GeneListFigure10.allergies) | 94 KB | Jun. 30, 2010 |
| TABLE 3D (GeneListFigure11.syst.ster) | 92 KB | Jun. 30, 2010 |
| TABLE 3E (GeneListFigure12.hyper) | 308 KB | Jun. 30, 2010 |
| TABLE 3F (GeneListFigure13.obesity) | 178 KB | Jun. 30, 2010 |
| TABLE 3G (GeneListFigure14.diabetes) | 143 KB | Jun. 30, 2010 |
| TABLE3H (GeneListFigure15.hyperlipidemia) | 163 KB | Jun. 30, 2010 |
| TABLE 31 (GeneListFigure16.lung) | 91 KB | Jun. 30, 2010 |
| TABLE 3J (GeneListFigure17.bladder) | 1117 KB | Jun. 30, 2010 |
| TABLE 3K (GeneListFigure18.bladder) | 931 KB | Jun. 30, 2010 |
| TABLE 3L (GeneListFigure19.cad) | 241 KB | Jun. 30, 2010 |
| TABLE 3M (GeneListFigure20.ra) | 322 KB | Jun. 30, 2010 |
| TABLE 3N (GeneListFigure2l.depression) | 150 KB | Jun. 30, 2010 |
| TABLE 30 (GeneListFigure22.ra) | 48 KB | Jun. 30, 2010 |
| TABLE 4 | 113 KB | Jun. 30, 2010 |

## SEQUENCE LISTING

**[0003]** The application includes a paper copy of the sequence listing submitted in the parent application, Ser. No. 10/601,518, filed on Jun. 20, 2003, the contents of which is hereby incorporated by reference.

## BACKGROUND

**[0004]** The blood is a vital part of the human circulatory system for the human body. Numerous cell types make up the blood tissue including monocytes, leukocytes, lymphocytes and erythrocytes. Although many blood cell types have been described, there are likely many as yet undiscovered cell types in the human blood. Some of these undiscovered cells may exist transiently, such as those derived from tissues and organs that are constantly interacting with the circulating blood in health and disease. Thus, the blood can provide an immediate picture of what is happening in the human body at any given time.

**[0005]** The turnover of cells in the hematopoietic system is enormous. It was reported that over one trillion cells, including 200 billion erythrocytes and 70 billing neutropilic leukocytes, turn over each day in the human body (Ogawa 1993). As a consequence of continuous interacts between the blood and the body, genetic changes that occur within the cells or tissues of the body will trigger specific changes in gene expression within blood. It is the goal of the present invention that these genetic alterations be harnessed for diagnostic and prognostic purposes, which may lead to the development of therapeutics for ameliorating disease.

**[0006]** For example, isoformic myosin heavy chain genes are known to be generally expressed in cardiac muscle tissue. In the rodent, the (MyHC gene is only highly expressed in the fetus and in diseased states such as overt cardiac hypertrophy, heart failure and diabetes, the (MyHC gene is highly expressed shortly after birth and continues to be expressed in the adult heart. In the human, however, (MyHC is highly expressed in the ventricles from the fetal stage through adulthood. This highly expressed (MyHC, which harbours several mutations, has been demonstrated to be involved in familial hypertrophic cardiomyopathy (Geisterfer-Lowrance et al. 1990). It was reported that mutations of (MyHC can be detected by PCR using blood lymphocyte DNA (Ferrie et al., 1992). Most recently, it was also demonstrated that mutations of the myosin-binding protein C in familial hypertrophic cardiomyopathy can be detected in the DNA extracted from lymphocytes (Niimura et al., 1998).

**[0007]** Similarly, APP and APC, which are known to be tissue specific and predominantly expressed in the brain and intestinal tract, are also detectable in the transcripts of blood. These cell- or tissue-specific transcripts are not detectable by Northern blot analysis. However, the low number of transcript copies can be detected by RT-PCR analysis. These findings strongly demonstrate that genes preferentially expressed in specific tissues can be detected by a highly sensitive RT-PCR assay. In recent years, evidence has been obtained to indicate that expression of cell or tissue-restricted genes can be detected in the certain peripheral nucleated blood cells of patients with metastatic transitional cell carcinoma (Yuasa et al. 1998) and patients with prostate cancer (Gala et al. 1998).

**[0008]** In the prior art, there is a need for large samples and/or costly and time-consuming separation of cell types within the blood (Kimoto (1998) and Chelly et al. (1989;

1988)). The prior art, however, is deficient in non-invasive methods of screening for tissue-specific diseases. The present invention fulfills this long-standing need and desire in the art.

## SUMMARY OF THE INVENTION

**[0009]** The present invention relates generally to the molecular biology of human diseases. More specifically, the present invention relates to a process using the genetic information contained in human peripheral whole blood for the diagnosis, prognosis and monitoring of genetic and infectious disease in the human body.

**[0010]** This present invention discloses a process of using the genetic information contained in human peripheral whole blood in the diagnosis, prognosis and monitoring of genetic and infectious disease in the human body. The process described herein requires a simple blood sample and is, therefore, non-invasive compared to conventional practices used to detect tissue specific disease, such as biopsies

**[0011]** The invention is based on the discovery that gene expression in the blood is reflective of body state and, as such, the resultant disruption of homeostasis under Conditions of disease can be detected through analysis of transcripts differentially expressed in the blood alone. Thus, the identification of several key transcripts or genetic markers in blood will provide information about the genetic state of the cells, tissues, organ systems of the human body in health and disease

**[0012]** The present invention demonstrates that a simple drop of blood may be used to determine the quantitative expression of various mRNAs that reflect the health/disease state of the subject through the use of RT-PCR analysis. This entire process takes about three hours or less. The single drop of blood may also be used for multiple RT-PCR analyses. It is believed that the present finding can potentially revolutionize the way that diseases are detected, diagnosed and monitored because it provides a non-invasive, simple, highly sensitive and quick screening for tissue-specific transcripts. The transcripts detected in Whole blood have potential as prognostic or diagnostic markers of disease, as they reflect disturbances in homeostasis in the human body. Delineation of the sequences and/or quantitation of the expression levels of these marker genes by RT-PCR will allow for an immediate and accurate diagnostic/prognostic test for disease or to assess the efficacy and monitor a particular therapeutic.

**[0013]** One object of the present invention is to provide a non-invasive method for the diagnosis, prognosis and monitoring of genetic and infectious disease in humans and animals.

**[0014]** In one embodiment of the present invention, there is provided a method for detecting expression of a gene in blood from a subject, comprising the steps of: a) quantifying RNA from a subject blood sample; and b) detecting expression of the gene in the quantified RNA, wherein the expression of the gene in quantified RNA indicates the expression of the gene in the subject blood. An example of the quantifying method is by mass spectrometry.

**[0015]** In another embodiment of the present invention, there is provided a method for detecting expression of one or more genes in blood from a subject, comprising the steps of: a) obtaining a subject blood sample; b) extracting RNA from the blood sample; c) amplifying the RNA; d) generating expressed sequence tags (ESTs) from the amplified RNA product; and e) detecting expression of the genes in the ESTs, wherein the expression of the genes in the ESTs indicates the expression of the genes in the subject blood. Preferably, the subject is a fetus, an embryo, a child, an adult or a non-human animal. The genes are non-cancer-associated and tissue-specific genes. Still preferably, the amplification is performed by RT-PCR using random sequence primers or gene-specific primers.

**[0016]** In still another embodiment of the present invention, there is provided a method for detecting expression of one or more genes in blood from a subject, comprising the steps of: a) obtaining a subject blood sample; b) extracting DNA fragments from the blood sample; c) amplifying the DNA fragments; and d) detecting expression of the genes in the amplified DNA product, wherein the expression of the genes in the amplified DNA product indicates the expression of the genes in the subject blood.

**[0017]** In yet another embodiment of the present invention, there is provided a method for monitoring a course of a therapeutic treatment in an individual, comprising the steps of: a) obtaining a blood sample from the individual; b) extracting RNA from the blood sample; c) amplifying the RNA; d) generating expressed sequence tags (ESTs) from the amplified RNA product: e) detecting expression of genes in the ESTs, wherein the expression of the genes is associated with the effect of the therapeutic treatment; and f) repeating steps a)-e), wherein the course of the therapeutic treatment is monitored by detecting the change of expression of the genes in the ESTs. Such a method may also be used for monitoring the onset of overt symptoms of a disease, wherein the expression of the genes is associated with the onset of the symptoms. Preferably, the amplification is performed by RT-PCR, and the change of the expression of the genes in the ESTs is monitored by sequencing the ESTs and comparing the resulting sequences at various time points, or by performing single nucleotide polymorphism analysis and detecting the variation of a single nucleotide in the ESTs at various time points.

**[0018]** In still yet another embodiment of the present invention, there is provided a method for diagnosing a disease in a test subject, comprising the steps of: a) generating a cDNA library for the disease from a whale blood sample from a normal subject; b) generating expressed sequence tag (EST) profile from the normal subject cDNA library; c) generating a cDNA library for the disease from a whole blood sample from a test subject; d) generating EST profile from the lest subject cDNA library; and e) comparing the test subject EST profile to the normal subject EST profile, wherein if the test subject EST profile differs from the normal subject EST profile, the test subject might be diagnosed with the disease.

**[0019]** In still yet another embodiment of the present invention, there is provided a kit for diagnosing, prognosing or predicting a disease, comprising: a) gene-specific primers; wherein the primers are designed in such a way that their sequences contain the opposing ends of two adjacent exons for the specific gene with the intron sequence excluded; and b) a carrier, wherein the carrier immobilizes the primer(s). Preferably, the gene-specific primers are selected from the group consisting of insulin-specific primers, atrial natriuretic factor-specific primers, zinc finger protein gene-specific primers, beta-myosin heavy chain gene-specific primers, amyloid precurser protein gene-specific primers, and adenomatous polyposis-coli protein gene-specific primers. Further preferably, the gene-specific primers are selected from the group consisting of SEQ ID Nos. 1 and 2; and SEQ ID Nos. 5 and 6. Such a kit may be applied to a test subject whole blood sample to diagnose, prognose or predict a disease by detecting the quantitative expression levels of specific

genes associated with the disease in the test subject and then comparing to the levels of same genes expressed in a normal subject. Such a kit may also be used for monitoring a course of therapeutic treatment or monitoring the onset of overt symptoms of a disease.

**[0020]** In yet another embodiment of the *sent invention, there is provided a kit for diagnosing, prognosing or predicting a disease, comprising: a) probes derived from a whole blood sample for a specific disease; and b) a carrier, wherein the carrier immobilizes the probes. Such a kit may be applied to a test subject whole blood sample to diagnose, prognose or predict a disease by detecting the quantitative expression levels of specific genes associated with the disease in the test subject and then comparing to the levels of same genes expressed in a normal subject. Such a kit may also be used for monitoring a course of therapeutic treatment or monitoring the onset of overt symptoms of a disease.

**[0021]** Furthermore, the present invention provides a cDNA library specific for a disease, wherein the cDNA library is generated from whole blood samples.

**[0022]** Other and further aspects, features, and advantages of the present invention will be apparent from the following description of the presently preferred embodiments of the invention. These embodiments are given for the purpose of disclosure.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0023]** The above-recited features, advantages and objects of the invention, as well as others which will become clear, are attained and can be understood in detail, more particular descriptions of the invention briefly summarized above may be had by reference to certain embodiments thereof which are illustrated in the appended drawings. These drawings form a part of the specification. It is to be noted, however, that the appended drawings illustrate preferred embodiments of the invention and therefore are not be considered limiting in their scope not be considered to limit the scope of the invention.

**[0024]** FIG. **1** shows the following RNA samples prepared from human blood; FIG. **1**A: Lane 1, Molecular weight marker; Lane 2, RT-PCR on APP gene; Lane 3, PCR on APP gene; Lane 4, RT-PCR on APC gene; Lane 5, PCR on APC gene; FIG. **1**B: Lanes 1 and 2, RT-PCR and PCR of (MyHC, respectively; Lanes 3 and 4, RT-PCR of (MyHC from RNA prepared from human fetal and human adult heart, respectively; Lane 5, Molecular weight marker.

**[0025]** FIG. **2** shows quantitative RT-PCR analysis performed on RNA samples extracted from a drop of blood. Forward primer (5'-GCCCTCTGGGGACCTGAC-3', SEQ ID No. 1) of exon 1 and reverse primer (5'-CCCACCTG-CAGGTCCTCT-3", SEQ ID No. 2) of exons 1 and 2 of insulin gene. Blood samples of 4 normal subjects were assayed. Lanes 1, 3, 5 and 7 represent overnight "fasting" blood sample and lanes 2, 4, 6 and 8 represent "non-fasting" samples.

**[0026]** FIG. **3** shows quantitative RT-PCR analysis performed on RNA samples extracted from a drop of blood. Lanes 1 and 2 represent normal healthy person and lane 3 represents late-onset diabetes (Type II) and lane 4 represents asymptomatic diabetes.

**[0027]** FIG. **4** shows multiple RT-PCR assay in a drop of blood. Primers were derived from insulin gene (INS), zinc-finger protein gene (ZFP) and house-keeping gene (GADH). Lane 1 represents normal person. Lane 2 represents late-onset diabetes and lane 3 represents asymptomatic diabetes.

**[0028]** FIG. **5** shows standardized levels of insulin gene (FIG. **5**A) and ZFP gene (FIG. **5**B) expressed in a drop of blood. The first three subjects were normal, second two subjects showed normal glucose tolerance, and the last subject had late onset diabetes type II. FIG. **5**C shows standardized levels of insulin gene expressed in each fractionated cell from whole blood

**[0029]** FIG. **6** shows the differential screening of human blood cell cDNA library with different cDNA probes of heart and brain tissue. FIG. **6**A shows blood cell cDNA probes vs. adult heart cDNA probes. FIG. **6**B shows blood cell cDNA probes vs. human brain cDNA probes.

**[0030]** FIG. **7** graphically shows the 1,800 unique genes in human blood and in the human fetal heart grouped into seven cellular functions.

**[0031]** FIG. **8** shows a diagrammatic representation of gene expression profiles of blood samples from individuals having both osteoarthritis and hypertension as compared with gene expression profiles from normal individuals.

**[0032]** FIG. **9** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having both osteoarthritis and who were obese as described herein as compared with gene expression profiles from normal individuals

**[0033]** FIG. **10** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having both osteoarthritis and allergies as described herein as compared with gene expression profiles from normal individuals.

**[0034]** FIG. **11** shows a diagrammatic representation of gene expression profiles of blood samples from individuals having osteoarthritis and who were subject to systemic steroids as described herein as compared with gene expression profiles from normal individuals.

**[0035]** FIG. **12** shows a diagrammatic representation of gene expression profiles of blood samples from individuals having hypertension as compared with gene expression profiles from samples of both non-hypertensive and normal individuals.

**[0036]** FIG. **13** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as obese as described herein as compared with gene expression profiles from normal and non-obese individuals

**[0037]** FIG. **14** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as hiving type 2 diabetes as described herein as compared with gene expression profiles from normal and non-type 2 diabetes individuals.

**[0038]** FIG. **15** shows 4 diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having hyperlipidemia as described herein as compared with gene expression profiles from normal and non-hyperlipidemia patients.

**[0039]** FIG. **16** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having lung disease as described herein as compared with gene expression profiles from normal and non lung disease individuals.

**[0040]** FIG. **17** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having bladder cancer as described herein as compared with gene expression profiles from non bladder cancer individuals.

**[0041]** FIG. **18** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having advanced stage bladder cancer or early stage bladder cancer as described herein as compared with gene expression profiles from non bladder cancer individuals

**[0042]** FIG. **19** shows a diagrammatic, representation of gene expression profiles of blood samples from individuals who were identified as having coronary artery disease (CAD) as described herein as compared with gene expression profiles from non-coronary artery disease individuals

**[0043]** FIG. **20** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having rheumatoid arthritis as described herein as compared with gene expression profiles from non-rheumatoid arthritis individuals.

**[0044]** FIG. **21** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having depression as described herein as compared with gene expression profiles from non-depression individuals.

**[0045]** FIG. **22** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having various stages of osteoarthritis as described herein as compared with gene expression profiles from normal individuals.

**[0046]** FIG. **23** shows RT-PCR of overexpressed genes in CAD peripheral blood cells identified using microarray experiments, including PBP, PF4 and F13A.

**[0047]** FIG. **24** shows the the "Blood Chip", a cDNA microarray slide with 10,368 PCR products derived from peripheral blood cell cDNA libraries. Colors represent hybridization to probes labeled mth Cy3 (green) or Cy5 (red). Yellow spots indicate common hybridization between both probes. In slide A, normal blood cell RNA samples were labeled with Cy3 and CAD blood cell RNA samples were labeled with Cy5. In slide B, Cy3 and Cy5 were switched to label the RNA samples. (Cluster analysis revealed distinct gene expression profiles for normal and CAD samples.)

## DETAILED DESCRIPTION

**[0048]** In accordance with the present invention, there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, e.g., Sambrook, Fritsch & Maniatis, "Molecular Cloning: A Laboratory Manual (1982); "DNA Cloning: A Practical Approach," Volumes I and II (D. N. Glover ed. 1985); "Oligonucleotide Synthesis" (M. J. Gait ed. 1984); "Nucleic Acid Hybridization" [B. D. Hames & S. J. Higgins eds. (1985)]; "Transcription and Translation" [B. D. Hames & S. J. Higgins eds. (1984)]; "Animal Cell Culture" [R. I. Freshney, ed. (1986)]; "Immobilized Cells And Enzymes" [IRL Press, (1986)]; B. Perbal, "A Practical Guide To Molecular Cloning" (1984). Therefore, if appearing herein, the following terms shall have the definitions set out below.

**[0049]** A "cDNA" is defined as copy-DNA or complementary-DNA, and is a product of a reverse transcription reaction from an mRNA transcript. "RT-PCR" refers to reverse transcription polymerase chain reaction and results in production of cDNAs that are Complementary to the mRNA template(s).

**[0050]** In addition to RT-PCR, other methods of amplifying may also be used for the purpose of measuring/quantitating tissue-specific transcripts in human blood. For example, mass spectrometry may be used to quantify the transcripts (Koster et al, 1996; Fu et al., 1998). The application of presently disclosed method for detecting tissue-specific transcripts in blood does not restrict to subjects undergoing course of therapy or treatment, it may also be used for monitoring a patient for the onset of overt symptoms of a disease. Furthermore, the present method may be used for detecting any gene transcripts in blood. A kit for diagnosing, prognosing or even predicting a disease may be designed using gene-specific primers or probes derived from a whole blood sample for a specific disease and applied directly to a drop of blood. A cDNA library specific for a disease may be generated from whole blood samples and used for diagnosis, prognosis or even predicting a disease.

**[0051]** The term "oligonucleotide" is defined as a molecule comprised of two or more deoxyribonucleotides and/or ribonucleotides, preferably more than three. Its exact size will depend upon many factors which, in turn, depend upon the ultimate function and use of the oligonucleotide. The upper limit may be 15, 20, 25, 30, 40 or 50 nucleotides in length. The term "primer" as used herein refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product, which is complementary to a nucleic acid strand, is induced, i.e., in the presence of nucleotides and an inducing agent such as a DNA polymerase and at a suitable temperature and pH. The primer may be either single-stranded or double-stranded and must be sufficiently long to prime the synthesis of the desired extension product in the presence of the inducing agent. The exact length of the primer will depend upon many factors, including temperature, source of primer and the method used. For example, for diagnostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains 15-25 or more nucleotides, although it may contain fewer nucleotides. The factors involved in determining the appropriate length of primer are readily known to one of ordinary skill in the art.

**[0052]** As used herein, random sequence primers refer to a composition of primers of random sequence, i.e. not directed towards a specific sequence. These sequences possess sufficient complementary to hybridize with a polynucleotide and the primer sequence need not reflect the exact sequence of the template.

**[0053]** "Restriction fragment length polymorphism" refers to variations in DNA sequence detected by variations in the length of DNA fragments generated by restriction endonuclease digestion.

**[0054]** A standard Northern blot assay can be used to ascertain the relative amounts of mRNA in a cell tissue obtained from plant or other tissue, in accordance with conventional Northern hybridization techniques known to those persons of ordinary skill in the art. The Northern blot uses a hybridization probe, e.g. radiolabelled cDNA, either containing the full-length, single stranded DNA or a fragment of that DNA sequence at least 20 (preferably at least 30, more preferably at least 50, and most preferably at least 100 consecutive nucleotides in length). The DNA hybridization probe can be labelled by any of the many different methods known to those skilled in this art. The labels most commonly employed for these studies are radioactive elements, enzymes, chemicals which fluoresce when exposed to ultraviolet light, and others. A number of fluorescent materials are known and can be

utilized as labels. These include, for example, fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow. A particular detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate. Proteins can also be labeled with a radioactive element or with an enzyme. The radioactive label can be detected by any of the currently available counting procedures. The preferred isotope may be selected from $^{3}H$, $^{14}C$, $^{32}P$, $^{33}S$, $^{36}Cl$, $^{51}Cr$, $^{57}Co$, $^{58}Co$, $^{59}Fe$, $^{90}Y$, $^{125}I$, $^{131}I$, and $^{106}Re$. Enzyme labels are likewise useful, and can be detected by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques. The enzyme is conjugated to the selected particle by reaction with bridging molecules such as carbodiimides, diisotyanates, glutaraldehyde and the like. Many enzymes which can be used in these procedures are known and can be utilized. The preferred are peroxidase, (-glucuronidase, (-D-glucosidase, (-D-galactosidase, urease, glucose oxidase plus peroxidase and alkaline phoiphatase. U.S. Pat. Nos. 3,654,090, 3,850,752, and 4,016,043 are referred to by way of example for their disclosure of alternate labeling material and methods.

**[0055]** As used herein, "individual" refers to human subjects as well as non-human subjects. The examples herein are not meant to limit the methodology of the present invention to human subjects only, as the instant methodology is useful in the fields of veterinary medicine, animal sciences and such.

**[0056]** As used herein, "detecting" refers to determining the presence of a gene expression product, for example cDNA, RNA or EST, by any method known to those of skill in the art or taught in numerous texts and laboratory manuals (see for example, Ausubel et al. Short Protocols in Molecular Biology (1995) 3rd Ed. John Wiley & Sons, Inc.). For example, methods of detection include but are not limited to, RNA fingerprinting, Northern blotting, polymerase chain reaction, ligase chain reaction, Qbeta replicase, isothermal amplification method, strand displacement amplification, transcription based amplification systems, nuclease protection (SI nuclease or RNAse protection assays) as well as methods disclosed in WO 88/10315, Wo 89/ 06700PCT/ US87/00880, PCT/ US89/0102

**[0057]** As used herein, a disease of the invention includes, but is not limited to, blood disorder, blood lipid disease, autoimmune disease, arthritis (including osteoarthritis, rheumatoid arthritis, lupus, allergies, juvenile rheumatoid arthritis and the like), bone or joint disorder, a cardiovascular disorder, obesity, respiratory disease, lung diseases, hyperlipidemias, endocrine disorder, immune disorder, infectious disease, muscle wasting and whole body wasting disorder, neurological disorders including neurodegenerative and/or neuropsychiatric diseases, mood disorders, skin disorder, kidney disease, scleroderma, stroke, hereditary hemorrhage telangiectasia, diabetes, disorders associated with diabetes. (e.g., PVD), hypertension, Gaucher's disease, cystic fibrosis, sickle cell anemia, liver disease, pancreatic disease, eye, ear, nose and/or throat disease, diseases affecting the reproductive organs, gastrointestinal diseases (including diseases of the colon, diseases of the spleen, appendix, gall bladder, and others) and the like. For further discussion of human diseases, see Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders by Victor A. McKusick (12th Edition (3 volume set) June 1998, Johns Hopkins University Press, ISBN: 0801857422) and Harrison's Principles of Internal Medicine by Braunwald, Fauci, Kasper, Hauser, Longo, & Jameson (15th Edition 2001), the entirety of which is incorporated herein.

**[0058]** In another embodiment of the invention, a disease refers to an immune disorder, such as those associated with overexpression of a gene or expression of a mutant gene (e.g., autoimmune diseases, such as diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), multiple sclerosis, encephalomyelitis, myasthenia gravis, systemit lupus erythematosis, automimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthnia, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing, loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Graves' disease, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis); graft-versus-host disease, cases of transplantation, and allergy.

**[0059]** In another embodiment, a disease of the invention is a cellular proliferative and/or differentiative disorder that includes, but is not limited to, cancer, e.g., carcinoma, sarcoma or other metastatic disorders and the like. As used herein, the term "cancer" refers to cells having the capacity for autonomous growth, i.e., an abnormal state of condition characterized by rapidly proliferating cell growth. "Cancer" is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. Examples of cancers include, but are nor limited to solid tumours and leukaemias, including: apudoma, choristoma, branchioma, malignant carcinoid syndrome, carcinoid heart disease, carcinoma (e.g., Walker, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumour, in situ, Krebs 2, Merkel cell, mucinous, non-small cell lung, oat cell papillary, scirrhous, bronchiolar, bronchogenic, squamous cell, and transitional cell), histiocytic disorders, leukaemia (e.g., B cell, mixed cell, null cell, T cell, chronic, HTLV-II-associated, lymphocytic acute, lymphocytic chronic, mast cell, and myeloid), histiocytosis malignant, Hodgkin disease, immunoproliferative small, non-Hodgkin lymphoma, plasmacytoma, reticuloendotheliosis, melanoma, chondroblastoma, chondroma, chondrosarcoma, fibroma, fibrosarcoma, giant cell tumours, histiocytoma, lipoma, liposarcoma, mesothelioma, myxoma, myxosarcoma, ostebma, osteosarcoma, Ewing sarcoma, synovioma, adenofibroma, adenolymphoma, carcinosarcoma, chordorna, craniopharyngioma, dysgerminoma, hamartoma, mesenchymoma, mesonephroma, Myosarcoma, ameloblastoma, cementoma, odontoma, teratoma, thymoma, trophoblastic tumour, adeno-carcinoma, adenoma, cholangioma, cholesteatoma, cylindroma, cystadenocarcinoma, cystadenoma, granulosa cell tumour, gynandroblastoma, hepatoma, hidradenoma, islet cell tumour, Leydig cell tumour, papilloma, Sertoli cell tumour, theca cell tumour, leiomyoma, leiomyosarcoma, myoblastoma, mymoma, myosarcoma, rhabdomyoma, rhabdomyosarcoma, ependymoma, ganglio-

neuroma, glioma, medulloblistoma, meningioma, neurilemmoma, neuroblastoma, neuroepithelioma, neurofibroma, neuroma, paraganglioma, paraganglioma nonchromaffin, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, angioma sclerosing, angiomatosis, glornangioma, hemangioendothelioma, hemangioma, hemangiopericytoma, henlanglosarcoma, lymphangioma, lymphangiomyoma; lymphangiosarcoma, pinealoma, carcinosarcoma, chondrosarcoma, cystosarcoma, phyllodes, fibrosarcoma, hemangiosarcoma, leimyosarcoma, leukosarccima, liposarcoma, lymphangiosarcoma, myosarcoma, myxosarcoma, ovarian carcinoma, rhabdomyosarcoma, sarcoma (e.g., Ewing, experimental, Kaposi, and mast cell), neoplasms (e.g., bone, breast, digestive system, colorectal, liver, pancreatic, pituitary, testicular, orbital, head and neck, central nervous system, acoustic, pelvic tespiratory tract, and urogenital), neurofibromatosis, and cervical dysplasia, and other conditions in which cells have become immortalised or transformed.

**[0060]** As used herein, a gene of the invention is a gene that is expressed in blood and is either upregulated, or downregulated and can be used, either solely or in conjunction with other genes, as a marker for disease as defined herein. The term "gene" includes a region that can be transcribed into RNA, as the invention contemplates detection of RNA or equivalents thereof, i.e., cDNA or EST. A gene of the invention includes but is not limited to genes specific for or involved in a particular biological process, such as apoptosis, differentiation, stress response, aging, proliferation, etc.; cellular mechanism genes, e.g. cell-cycle, signal transduction, metabolism of toxic compounds, and the like; disease associated genes, e.g. genes involved in cancer, schizophrenia; diabetes, high blood pressure, atherosclerosis, viral-host interaction and infection and the like.

**[0061]** For example, the gene of the invention can be an oncogene Manahan, D. and R. A. Weinberg, Cell (2000) 100:57; and Yokota, J., Carcinogenesis (2000) 21(3):497-503) whose expression within a cell induces that, cell to become converted from a normal cell into a tumor cell. Further examples of genes of the invention include, but are not limited to, cytokine genes (Rubinstein, M., et al., Cytokine Growth Factor Rev. (1998) 9(2):175-81); idiotype (Id) protein genes (Benezra, R., et al., Oncogene (2001) 20(58):8334-41; Norton, J. D., J. Cell Sci. (2000) 113(22):3897-905); prion genes (Prusiner, S. B., et al., Cell (1998) 93(3):337-48; Safar, J., and S. B. Prusiner, Prog. Brain Res. (1998) 117:421-34); genes that express Molecules that induce angiogenesis (Gould, V. E. and B. M. Wagner, Hum. Pathol. (2002) 33(11): 1061-3); genes encoding adhesion molecules (Chothia, C. and E. Y. Jones, Annu. Rev. Biochem. (1997) 66:823-62; Parise, L. V., et al., Semin. Cancer Biol. (2000) 10(6):407-14); genes encoding cell surface receptors (Deller, M. C., and Y. E. Jones, Curr. Opin. Struct. Biol. (2000) 10(2):213-9); genes of proteins that are involved in metastasizing and/or invasive processes (Boyd, D., Cancer Metastasis Rev. (1996) 15(1):77-89; Yokota, J., Carcinogenesis (2000) 21(3):497-503); genes of proteases as well as of molecules that regulate apoptosis and the cell cycle (Matrisian, L. M., Curr. Biol. (1999) 9(20):R776-8; Krepela, E., Neoplasma (2001) 48(5): 332-49; Basbaum and Werb, Curr. Opin. Cell Biol. (1996) 8:731-738; Birkedal-Hansen, et al., Crit. Rev. Oral Biol. Med. (1993) 4:197-250; Mignatti and Rifkin, Physiol. Rev. (1993) 73:161-195; Stetler-Stevenson, et al., Annu. Rev. Cell Biol. (1993) 9:541-573; Brinkerhoff, B., and L. M. Matrisan, Nature Reviews (2002) 3:207-214; Strasser, A., et al., Annu. Rev. Biochem. (2000) 69:217-45; Chao, D. T. and S. J. Korsmeyer, Annu. Rev. Immunol. (1998) 16:395-419; Mullauer, L., et al., Mutat. Res. (2001) 488(3):211-31; Fotedar, R., et al., Prog. Cell Cycle Res. (1996) 2:147-63; Reed, J. C., Am. J. Pathol. (2000) 157(5):1415-30; D'Ari, R., Bioassays (2001) 23(7):563-5); or multi-drug resistance genes, such as MDR1 gene (Childs, S, and V. Ling, Imp. Adv. Oncol. (1994) 21-36). In another embodiment, a gene of the invention contains a sequence found in Tables 2 or 3 or FIGS. **22-36**.

Construction of a Microarray

**[0062]** A nucleic acid microarray (RNA, DNA, cDNA, PCR products or ESTs) according to the invention was constructed as follows.

**[0063]** Nucleic acids (RNA, DNA, cDNA, PCR products or ESTs) (~40 ul) are precipitated with 4 ul (1/10 volume) of 3M sodium acetate (p1-1 5.2) and 100 ul (2.5 volumes) of ethanol and stored overnight at −20° C. They are then centrifuged at 3,300 rpm at 4° C. for 1 hour. The obtained pellets were washed with 50 ul ice-cold 70% ethanol and centrifuged again for 30 minutes. The pellets are then air-dried and resuspended well in 50% dimethylsulfoxide (DMSO) or 20 ul 3×SSC overnight. The samples are then deposited either singly or in duplicate onto Gamma Amino Propyl Silane (Corning CMT-GAPS or CMT-GAP2, Catalog No. 40003, 40004) or polylysine-coated slides (Sigma Cat. No. P0425) using a robotic GMS 417 or 427 arrayer (Affymetrix, CA). The boundaries of the DNA spots on the microarray are marked with a diamond scriber. The invention provides for arrays where 10-20,000 different DNAs are spotted onto a solid support to prepare an array, and also may include duplicate or triplicate DNAs.

**[0064]** The arrays are rehydrated by suspending the slides over a dish of warm particle free ddH2O for approximately one minute (the spots will swell slightly but not run into each other) and snap-dried on a 70-80° C. inverted heating block for 3 seconds. DNA is then UV crosslinked to the slide (Stratagene, Stratalinker, 65 mJ—set display to "650" which is 650×100 uJ) or baked at 80 C for two to four hours. The arrays are placed in a slide rack. An empty slide chamber is prepared and filled with the following solution: 3.0 grams of succinic anhydride (Aldrich) is dissolved in 189 ml of 1-methyl-2-pyrrolidinone (rapid addition of reagent is crucial), immediately after the last flake of succinic anhydride dissolved, 21.0 ml of 0.2 M sodium borate is mixed in and the solution is poured into the slide chamber. The slide rack is plunged rapidly and evenly in the slide chamber and vigorously shaken up and down for a few seconds, making sure the slides never leave the solution, and then mixed on an orbital shaker for 15-20 minutes. The slide rack is then gently plunged in 95° C. $ddH_20$ for 2 minutes, followed by plunging five times in 95% ethanol. The slides are then air dried by allowing excess ethanol to drip onto paper towels. The arrays are then stored in the slide box at room temperature until use.

Microarrays

**[0065]** Nucleic Acid Microarrays

**[0066]** Any combination of the nucleic acid sequences generated from nucleotides complimentary to regions of DNA expressed in blood are used for the construction of a microarray. In one embodiment, the microarray is chondrocyte-specific and encompasses genes which are important in the

osteoarthritis disease process. A microarray according to the invention preferably comprises between 10, 100, 500, 1000, 5000, 10,000 and 15,000 nucleic acid members, and more preferably comprises at least 5000 nucleic acid members. The nucleic acid members are known or novel nucleic acid sequences described herein, or any combination thereof. A microarray according to the invention is used to assay for differential gene expression profiles of genes in blood samples from healthy patients as compared to patient with a disease.

Microarray According to the Invention

GeneChip®

**[0067]** GeneChip® probe arrays are manufactured through a unique and robust process—a combination of photolithography and combinatorial chemistry—that results in many of the arrays' powerful capabilities. With a calculated minimum number of synthesis steps, GeneChip technology produces arrays with hundreds of thousands of different probes packed at an extremely high density. This feature enables researchers to obtain high quality, genome-wide data using small sample volumes. Manufacture is scalable because the length of the probes, not their number, determines the number of synthesis steps required. This robust and automated production process yields arrays with highly reproducible properties, which reduces user set-up time by eliminating the need for individual labs to produce and test their own arrays.

**[0068]** Using technologies adapted from the semiconductor industry, GeneChip manufacturing begins with a 5-inch square quartz wafer. Initially the quartz is washed to ensure uniform hydroxylation across its surface. Because quartz is naturally hydroxylated, it provides an excellent substrate for the attachment of chemicals, such as linker molecules, that are later used to position the probes on the arrays.

**[0069]** The wafer is placed in a bath of silane, which reacts with the hydroxyl groups of the quartz, and forms a matrix of covalently linked molecules. The distance between these sliane molecules determines the probes' packing density, allowing arrays to hold over 500,000 probe locations, or features, within a mere 1.28 square centimeters. Each of these features harbors millions of identical DNA molecules. The silane film provides a uniform hydroxyl density to initiate probe assembly. Linker molecules, attached to the silane matrix, provide a surface that may be spatially activated by light.

**[0070]** Probe synthesis occurs in parallel, resulting in the addition of an A, C, T, or G nucleotide to multiple growing chains simultaneously. To define which oligonucleotide chains will receive a nucleotide in each step, photolithographic masks, carrying 18 to 20 square micron windows that correspond to the dimensions of individual features, are placed over the coated wafer. The windows are distributed over the mask based on the desired sequence of each probe. When ultraviolet light is shone over the mask in the first step of synthesis, the exposed linkers become deprotected and are available for nucleotide coupling. Critical to this step is the precise alignment of the mask with the wafer before each synthesis step. To ensure that this critical step is accurately completed, chrome marks on the wafer and on the mask are perfectly aligned.

**[0071]** Once the desired features have been activated, a solution containing a single type of deoxynucleotide with a removable protection group is flushed over the wafer's surface. The nucleotide attaches to the activated linkers, initiating the synthesis process.

**[0072]** Although the process is highly efficient, some activated molecules fail to attach the new nucleotide. To prevent these "outliers" from becoming probes with missing nucleotides, a capping step is used to truncate them. In addition, the side chains of the nucleotides are protected to prevent the formation of branched oligonucleotides.

**[0073]** In the following synthesis step, another mask is placed over the wafer to allow the next round of deprotection and coupling. The process is repeated until the probes reach their full length, usually 25 nucleotides.

**[0074]** Although each position in the sequence of an oligonucleotide can be occupied by 1 of 4 nucleotides, resulting in an apparent need for 25×4, or 100, different masks per wafer, the synthesis process can be designed to significantly reduce this requirement. Algorithms that help minimize mask usage calculate how to best coordinate probe growth by adjusting synthesis rates of individual probes and identifying situations when the same mask can be used multiple times.

**[0075]** Once the synthesis is complete, the wafers are deprotected, diced, and the resulting individual arrays are packaged in flowcell cartridges. Depending on the number of probe features per array, a single wafer can yield between 49 and 400 arrays.

**[0076]** The manufacturing process ends with a comprehensive series of quality control tests. Additionally, a sampling of arrays from every wafer is used to test the batch by running control hybridizations. A quantitative test of hybridization is also performed using standardized control probes.

**[0077]** After passing these rigorous tests, GeneChip probe arrays are well prepared to help pursue ambitious goals ranging from the discovery of basic biological mechanisms to the development of new disease therapies.

The Human Genome U133 Set

**[0078]** The Human Genome U133 (HG-U133) Set, consisting of two GeneChip® arrays, contains almost 45,000 probe sets representing more than 39,000 transcripts derived from approximately 33,000 well-substantiated human genes. This set design uses sequences selected from GenBank®, dbEST, and RefSeq.

**[0079]** The sequence clusters were created from the UniGene database (Build 133, Apr. 20, 2001). They were then refined by analysis and comparison with a number of other publicly available databases including the Washington University EST trace repository and the University of California, Santa Cruz Golden Path human genome database (April 2001 release).

**[0080]** The HG-U133A Array includes representation of the RefSeq database sequences and probe sets related to sequences previously represented on the Human Genome U95Av2 Array. The HG-U133B Array contains primarily probe sets representing EST clusters.

15 K Chondrochip (Version 2b)

**[0081]** The Chondrochip version 2b is chondrocyte-specific microarray chip comprising 15000 novel and known EST sequences of the chondrocyte from chondrocyte-specific cDNA libraries.

Controls on the Chondrochip

**[0082]** There are two types of controls used on microarrays. First, positive controls are genes whose expression level is invariant between different stages of investigation and are used to monitor.

**[0083]** a) target DNA binding to the slide,

**[0084]** b) quality of the spotting and binding processes of the target DNA onto the slide,

**[0085]** c) quality of the RNA samples, and

**[0086]** d) efficiency of the reverse transcription and fluorescent labelling of the probes.

**[0087]** Second, negative controls are external controls derived from an organism unrelated to and therefore unlikely to cross-hybridize with the sample of interest. These are used to monitor for:

**[0088]** a) variation in background fluorescence on the slide, and

**[0089]** b) non-specific hybridization.

There are currently 63 controls spots on the ChondroChip™ consisting of:

| Type | No. |
|---|---|
| Positive Controls: | 2 |
| Alien DNA | 12 |
| *A. thaliana* DNA | 10 |
| Spotting Buffer | 41 |

Blood Chip

**[0090]** The "Blood chip" is a cDNA microarray slide with 10,368 PCR products derived from peripheral blood cell cDNA libraries as shown in FIG. **24**.

Target Nucleic Acid Preparation and Hybridization

**[0091]** Preparation of Fluorescent DNA Probe from mRNA

**[0092]** Fluorescently labeled target nucleic acid samples are array of the invention.

**[0093]** 2 μg Oligo-dT primers are annealed to 2ug of mRNA isolated from a blood sample of a patient in a total volume of 15 ul, by heating to 70° C. for 10 min, and cooled on ice. The mRNA is reverse transcribed by incubating the sample 42° C. for 1.5-2 hours in a 100 μl volume containing a final concentration of 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM MgCl2, 25 mM DTT, 25 mM unlabeled dNTPs, 400 units of Superscript II (200 U/uL, Gibco BRL), and 15 mM of Cy3 or Cy5 (Amersham). RNA is then degraded by addition of 15 μl of 0.1N NaOH, and incubation at 70° C. for 10 min. The reaction mixture is neutralized by addition of 15 μl of 0.1N HCL, and the volume is brought to 500 μl with TE (10 mM Tris, 1 mM EDTA), and 20 μg of Cot1 human DNA (Gibco-BRL) is added.

**[0094]** The labeled target nucleic acid sample is purified by centrifugation in a Centricon-30 micro-concentrator (Amicon). If two different target nucleic acid samples (e.g., two samples derived from a healthy patient vs patient with a disease) are being analyzed and compared by hybridization to the same array, each target nucleic acid sample is labeled with a different fluorescent label (e.g., Cy3 and Cy5) and separately concentrated. The separately concentrated target nucleic acid samples (Cy3 and Cy5 labeled) are combined into a fresh centricon, washed with 500 μl TE, and concentrated again to a volume of less than 7 μl. 1 μL of 10 μg/μl polyA RNA (Sigma, #P9403) and 1 μl of 10 μg/ul tRNA (Gibco-BRL, #15401-011) is added and the volume is adjusted to 9.5 μl with distilled water. For final-target nucleic acid preparation 2.1 μl 20×SSC (1.5M NaCl, 150 mM NaCitrate (pH8:0)) and 0.35 μl 10% SDS is added.

**[0095]** Hybridization

**[0096]** Labeled nucleic acid is denatured by heating for 2 min at 100° C., and incubated at 37° C. for 20-30 min before being placed on a nucleic acid array under a 22 mm×22 mm glass cover slip. Hybridization is carried out at 65° C. for 14 to 18 hours in a custom slide chamber with humidity maintained by a small reservoir of 3×SSC. The array is washed by submersion and agitation for 2-5 min in 2×SSC with 0.1% SDS, followed by 1×SSC, and 0.1×SSC. Finally, the array is dried by centrifugation for 2 min in a slide rack in a Beckman GS-6 tabletop centrifuge in Microplus carriers at 650 RPM for 2 min.

**[0097]** Signal Detection and Data Generation

**[0098]** Following hybridization of an array with one or more labeled target nucleic acid samples, arrays are scanned immediately using a GMS Scanner 418 and Scanalyzer software (Michael Eisen, Stanford University), followed by GeneSpring software (Silicon Genetics, CA) analysis. Alternatively, a GMS Scanner 428 and Jaguar software may be used followed by GeneSpring software analysis.

**[0099]** If one target nucleic acid sample is analyzed, the sample is labeled with one fluorescent dye (e.g., Cy3 or Cy5).

**[0100]** After hybridization to a microarray as described herein, fluorescence intensities at the associated nucleic acid members on the microarray are determined from images taken with a custom confocal microscope equipped with laser excitation sources and interference filters appropriate for the Cy3 or Cy5 fluors.

**[0101]** The presence of Cy3 or Cy5 fluorescent dye on the microarray indicates hybridization of a target nucleic acid and a specific nucleic acid member on the microarray. The intensity of Cy3 or Cy5 fluorescence represents the amount of target nucleic acid which is hybridized to the nucleic acid member on the microarray, and is indicative of the expression level of the specific nucleic acid member sequence in the target sample.

**[0102]** After hybridization, fluorescence intensities at the associated nucleic acid members on the microarray are determined from images taken with a custom confocal microscope equipped with laser excitation sources and interference filters appropriate for the Cy3 and Cy5 fluors. Separate scans are taken for each fluor at a resolution of 225 $\mu m^2$ per pixel and 65,536 gray levels. Normalization between the images is used to adjust for the different efficiencies in labeling and detection with the two different fluors. This is achieved by manual matching of the detection sensitivities to bring a set of internal control genes to nearly equal intensity followed by computational calculation of the residual scalar required for optimal intensity matching for this set of genes.

**[0103]** The presence of Cy3 or Cy5 fluorescent dye on the microarray indicates hybridization of a target nucleic acid and a specific nucleic acid member on the microarray. The intensities of Cy3 or Cy5 fluorescence represent the amount of target nucleic acid which is hybridized to the nucleic acid member on the microarray, and is indicative of the expression level of the specific nucleic acid member sequence in the target sample. If a nucleic acid member on the array shows no color, it indicates that the gene in that element is not expressed in either sample. If a nucleic acid member on the array shows a single color, it indicates that a labeled gene is expressed only in that cell sample. The appearance of both colors indicates that the gene is expressed in both tissue samples. The ratios of

Cy3 and Cy5 fluorescence intensities, after normalization, are indicative of differences of expression levels Of the associated nucleic acid member sequence in the two samples for comparison. A ratio of expression not equal to is used as an indication of differential gene expression.

**[0104]** The array is scanned in the Cy 3 and Cy5 channels and stored as separate 16-bit TIFF images. The images are incorporated and-analysed using Scanalyzer software which includes a gridding process to capture the hybridization intensity data from each spot on the array. The fluorescence intensity and background-subtracted hybridization intensity of each spot is collected and a ratio of measured mean intensities of Cy5 to Cy3 is calculated. A liner regression approach is used for normalization and assumes that a scatter plot of the measured Cy5 versus Cy3 intensities should have a scope of one. The average of the ratios is calculated and used to rescale the data and adjust the slope to one. A post-normalization cutoff of a ratio not equal to 1.0 is used to identify differentially exorcised genes.

**[0105]** When comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true. A small probability can be defined as the accepted threshold level at which the results being compared are considered significantly different. The accepted lower threshold is set at, but not limited to, 0.05 (i.e., there is a 5% likelihood that the results would be observed between two or more identical populations) such that any values determined by statistical means at or below this threshold are considered significant.

**[0106]** When comparing two or more samples for similarities, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true. A small probability can be defined as the accepted threshold level at which the results being compared are considered significantly different. The accepted lower threshold is set at, but not limited to, 0.05 (i.e., there is a 5% likelihood that the results would be observed between two or more identical populations) such that any values determined by statistical means above this threshold are not considered significantly different and thus similar.

**[0107]** Identification of genes differentially expressed in blood samples from patients with disease as compared to healthy patients is determined by statistical analysis of the gene expression profiles from healthy patient compared to patients with a disease using the Wilcox Mann Whitney rank sum test.

**[0108]** Data Acquisition and Analysis of Differentially Expressed EST Sequences

**[0109]** The differentially expressed EST sequences are then searched against available databases, including the "nt", "nr", "est", "gss" and"htg" databases available through NCBI to determine putative identities for ESTs matching to known genes or other ESTs. Functional characterization of ESTs with known gene matches are made according to any known method. Preferably, differentially expressed EST sequences are compared to the non-redundant Genbank/EMBL/DDBJ and dbEST databases using the BLAST algorithm (Altschul S F, Gish W, Miller W, Myers E W, Lipman D J. Basic local alignment search tool. J Mol Biol 1990; 215:403-10). A minimum value of $P=10^{-10}$ and nucleotide sequence identity >95%, where the sequence identity is non-contiguous or scattered, are required for assignments of putative identities for ESTs matching to known genes or to other EST. Construction of a non-redundant list of genes represented in the EST set is done with the help of Unigene, Entrez. and PubMed at the National Center for Biotechnology Information (NCBI) web site at www.ncbi.nlm.nih.gov.

**[0110]** Genes are identified from ESTs according to known methods. To identify novel genes from an EST sequence, the EST should preferably be at least 100 nucleotides in length, and more preferably 150 nucleotides in length, for annotation. Preferably, the EST exhibits open reading frame characteristics (i.e., can encode a putative polypeptide).

**[0111]** Because of the completion of the Human Genome Project, a specific EST which Matches with a genomic sequence can be mapped onto a specific chromosome based on the chromosomal location of the genomic sequence. However, no function may be known for the protein encoded by the sequence and the EST would then be considered "novel" in a functional sense. In one aspect, the invention is used to identify a novel differentially expressed EST, which is part of a larger known sequence for which no function is known, is used to determine the function of a gene comprising the EST. Alternatively, or additionally, the EST can be used to identify an mRNA or polypeptide encoded by the larger sequence as a diagnostic or prognostic marker of a disease.

**[0112]** Having identified an EST corresponding to a larger sequence, other portions of the larger sequence which comprises the EST can be used in assays to elucidate gene function, e.g., to isolate polypeptides encoded by the gene, to generate antibodies specifically reactive with these polypeptides, to identify binding partners of the polypeptides (receptors, ligands, agonists, antagonists and the like) and/or to detect the expression of the gene (or lack thereof) in healthy or diseased individuals.

**[0113]** In another aspect, the invention provides for nucleic acid sequences that do not demonstrate a "significant match" to any of the publicly known sequences in sequence databases at the time a query is done. Longer genomic segments comprising these types of novel EST sequences can be identified by probing genomic libraries, while longer expressed sequences can be identified in cDNA libraries and/or by performing polymerase extension reactions (e.g., RACE) using EST sequences to derive primer sequences as is known in the art. Longer fragments can be mapped to particular chromosomes by FISH and other techniques and their sequences compared to known sequences in genomic and/or expressed sequence databases.

**[0114]** The amino acid sequences encoded by the ESTs can also be used to search databases, such as GenBank, SWISS-PROT, EMBL database, PIR protein database, Vecbase, or GenPept for the amino acid sequences of the corresponding full-length genes according to procedures well known in the art.

**[0115]** Identified genes can be catalogued according to their putative function. Functional characterization of ESTs with known gene matches is preferably made according to the categories described by Hwang et al Compendium of Cardiovascular Genes. Circulation 1997; 96:4146-203. The distribution of genes in each of the subcellular categories will provide important insights into the disease process.

**[0116]** Alternative methods for analyzing ESTs are also available. For example, the ESTs may be assembled into contigs with sequence, alignment, editing, and assembly pro-

grams such as PHRED and PHRAP (Ewing, et al., 1998, *Genome Res.* 3:175, incorporated herein; and the web site at bozeman.genome.washington.edu). Contig redundancy is reduced by clustering nonoverlapping sequence contigs using the EST done identification number, which is common for the nonoverlapping 5 and 3 sequence reads for a single EST cDNA clone. In one aspect, the consensus sequence from each cluster is compared to the non-redundant Genbank/EMBL/DDBJ and dbEST databases using the BLAST algorithm with the help of unigene, Entrez and PubMed at the NCBI site.

**[0117]** Known Nucleic Acid Sequences or ESTs and Novel Nucleic Acid Sequences or ESTs

**[0118]** An EST that exhibits a significant match (>65%, and preferably 90% or greater, identity) to at least one existing sequence in an existing nucleic acid sequence database is characterized as a "known" sequence according to the invention. Within this category, some known ESTs match to existing sequences which encode polypeptides with known function(s) and are referred to as a "known sequence with a function". Other "known" ESTs exhibit a significant match to existing sequences which encode polypeptides of unknown function(s) and are referred to as a "known sequence with no known function",

**[0119]** EST sequences which have no significant match (less than 65% identity) to any existing sequence in the above cited available databases arc categorized as novel ESTs. To identify a novel gene from an EST sequence, the EST is preferably at least 150 nucleotides in length. More preferably, the EST encodes at least part of an open reading frame, that is, a nucleic acid sequence between a translation initiation codon and a termination codon, which is potentially translated into a polypeptide sequence.

**[0120]** The following references were cited herein:

**[0121]** Claudio J O et al. (1998). *Genomics* 50:44-52.

**[0122]** Chelly J et al. (1989). *Proc. Nat. Aced. Sci. USA.* 86:2617-2621.

**[0123]** Chelly 1 et al. (1988). *Nature* 333:858-860.

**[0124]** Drews J & Ryser S (1997). *Nature Biotech.* 15:1318-9.

**[0125]** Ferrie R M et al. (1992). *Am. J. Hum. Genet.* 51:251-62.

**[0126]** Fu D-J et al. (1998). *Nat. Biotech* 16: 381-4.

**[0127]** Gala J L et al. (1998). *Clin. Chem.* 44(3):472-81

**[0128]** Geisterfer-Lowrance A A T et al. (1990). *Cell* 62:999-1006

**[0129]** Groden J. et al. (1991). *Cell* 66:589-600.

**[0130]** Hwang D M et al. (1997). *Circulation* 96:4146-4203.

**[0131]** Jandreski M A & Liew C C (1987). *Hum. Genet.* 76:47-53.

**[0132]** Jin O et al. (1990). *Circulation* 82:8-16

**[0133]** Kimoto Y (1998). *Mol. Gen. Genet* 258:233-239.

**[0134]** Koster M et al. (1996). *Nat. Biotech* 14: 1123-8.

**[0135]** Liew & Jandreski (1986). *Proc. Nat. Acad. Sci. USA.* 83:3175-31

**[0136]** Liew C C et al. (1990). *Nucleic Acids Res.* 18:3647-3651.

**[0137]** Liew C C (1993). *J Mol. Cell. Cardiol.* 25:891-894

**[0138]** Liew C C et al. (1994). *Proc. Natl. Acad. Sci. USA.* 91:10645-10649.

**[0139]** Liew et al. (1997). *Mol. and Cell. Biochem.* 172:81-87.

**[0140]** Niimura H et al. (1998). *New Eng. J. Med.* 338: 1248-1257.

**[0141]** Ogawa M (1993). *Blood* 81:2844-2853.

**[0142]** Santoro I M & Groden J (1997). *Cancer Res.* 57:488-494.

**[0143]** Yuasp T et al. (1998). *Japanese J. Cancer Res.* 89:879-81

Description of Tables:

**[0144]** Table 1: Overlap of Genes Expressed in Blood

**[0145]** (Estimated from limited known genes of about 1,800 as derived from the database of 6,297 ESTs from human blood cell library).

**[0146]** Table 2: Comparison of 1,800 Unique Genes Identified in the Blood Cell cDNA

**[0147]** Library to Genes Previously Identified in Specific Tissues

**[0148]** Column 1: List of unique genes derived from 6,283 known ESTs from blood cells. Column 2: Number of genes found in randomly sequenced ESTs from blood cells. Column 3: Accession number. Column 4: "+" indicates the presence of the unique gene in publicly available cDNA libraries of blood (Bl), brain (Br), heart (H), kidney (K), liver (Li) and lung (Lu).

**[0149]** **Comparison to previously identified tissue-specific genes was determined using the GenBank of the National Centre of Biotechnology Information (NCBI) Database.

**[0150]** Table 3: Genes that are differentially expressed in blood samples from patients with different diseases as compared to blood samples from healthy patients.

**[0151]** Table 3A shows the identity of those genes that are differentially expressed in blood samples from patients with osteoarthritis and hypertension as depicted in FIG. **8**

**[0152]** Table 3B shows the identity of those genes that are differentially expressed in blood samples from patients with osteoarthritis and obesity as depicted in FIG. **9**.

**[0153]** Table 3C shows the identity of those genes that are differentially expressed in blood samples from patients with osteoarthritis and allergies as depicted in FIG. **10**.

**[0154]** Table 3D shows the identity of those genes that are differentially expressed in blood samples from patients with osteoarthritis and subject to systemic steroids as depicted in FIG. **11**.

**[0155]** Table3E shows the identity of those genes that are differentially expressed in blood samples from patients with hypertension as depicted in FIG. **12**.

**[0156]** Table 3F shows the identity of those genes that are differentially expressed in blood samples from patients obesity as depicted in FIG. **13**.

**[0157]** Table 3G shows the identity of those genes that are differentially expressed in blood samples from patients with type II diabetes as depicted in FIG. **14**.

**[0158]** Table 3H shows the identity of those genes that are differentially expressed in blood samples from patients with hyperlipidemia as depicted in FIG. **15**.

**[0159]** Table 3I shows the identity of those genes that are differentially expressed in blood samples from patients with lung disease as depicted in FIG. **16**.

**[0160]** Table 3J shows the identity of those genes that are differentially expressed in blood samples from patients with bladder cancer as depicted in FIG. **17**.

**[0161]** Table 3K shows the identity of those genes that are differentially expressed in blood samples from patients with bladder cancer as depicted in FIG. **18**.

**[0162]** Table 3L shows the identity of those genes that are differentially expressed in blood samples from patients with coronary artery disease (CAD) as depicted in FIG. **19**.

**[0163]** Table 3M shows the identity of those genes that are differentially expressed in blood samples from patients with rheumatoid arthritis as depicted in FIG. **20**.

**[0164]** Table 3N shows the identity of those genes that are differentially expressed in blood samples from patients with depression as depicted in FIG. **21**.

**[0165]** Table 3O shows the identity of those genes that are differentially expressed in blood samples from patients with various stages of osteoarthritis as depicted in FIG. **22**.

**[0166]** Table 4 shows 102 EST sequences of Tables 3A-3O with "no-significant match" to known gene sequences.

**[0167]** Table 5 shows a list of genes showing greater than two fold differential expression in CAD peripheral blood cells vs normal blood cells.

**[0168]** The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion.

## EXAMPLE 1

**[0169]** Construction of cDNA Library

**[0170]** RNA extracted from human tissues (including fetal heart, adult heart, liver, brain, prostate gland and whole blood) were used to construct unidirectional cDNA libraries. The first mammalian heart cDNA library was constructed as early as 1982. Since then, the methodology has been revised and optimal conditions have been developed for construction of human heart and hematopoietic progenitor cDNA libraries (Liew et al., 1984; Liew 1993, Claudio et al., 1998). Most of the novel genes which were identified by sequence annotation can now be obtained as full length transcripts.

## EXAMPLE 2

Catalogue of EST Database

**[0171]** Random partial sequencing of expressed sequence tags (ESTs) of cDNA clones from the blood cell library was carried out to establish an EST database of blood. The known genes as derived from the ESTs were categorized into seven major cellular functions (Hwang, Dempsey et al., 1997). The preparation of the chondrocyte-specific EST database is reported in WO 02/070737, which is hereby incorporated by reference in its entirety.

## EXAMPLE 3

**[0172]** Differential Screening of cDNA Library

**[0173]** cDNA probes generated from transcripts of each tissue were used to hybridize the blood cell cDNA clones or chondrocyte cDNA clones (Liew et al., 1997; WO 02/070737). The "positive" signals which were hybridized with P-labelled cDNA probes were defined as genes which shared identity with blood and respective tissues. The "negative" spots which were not exposed to P-labelled cDNA probes were considered to be blood-cell-enriched or low frequency transcripts.

## EXAMPLE 4

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) Assay

**[0174]** RNA extracted from samples of human tissue was used for RT-PCR analysis (Jin et al. 1990). Three pairs of forward and reverse primers were designed for human cardiac beta-myosin heavy chain gene ((MyHC), amyloid precurser protein (APP) gene and adenomatous polyposis-coli protein (APC) gene. The PCR products were also subjected to automated DNA sequencing to verify the sequences as derived from the specific transcripts of blood.

## EXAMPLE 5

Detection of Tissue Specific Gene Expression in Human Blood Using RT-PCR

**[0175]** The beta-myosin heavy chain gene ((MyHC) transcript (mRNA) is known to be highly expressed in ventricles of the human heart. This sarcomeric protein is important for heart muscle contraction and its presence would not be expected in other non-muscle tissues and blood. In 1990, the gene for human cardiac (MyHC was completely sequenced (Liew et al. 1990) and was comprised of 41 exons and 42 introns.

**[0176]** The method of reverse transcription polymerase chain reaction (RT-PCR) was used to determine whether this cardiac specific mRNA is also present in human blood. A pair of primers was designed; the forward primer (SEQ ID No. 3) was on the boundary of exons 21 and 22, and the reverse primer (SEQ ID No. 4) was on the boundary of exons 24 and 25. This region of mRNA is only present in (MyHC and is not found in the alpha-myosin heavy chain gene ((MyHC).

**[0177]** A blood sample was first treated with lysing buffer and then undergone centrifuge. The resulting pellets were further processed with RT-PCR. RT-PCR was performed using the total blood cell RNA as a template. A nested PCR product was generated and used for sequencing. The sequencing results were subjected to BLAST and the identity of exons 21 to 25 was confirmed to be from (MyHC (FIG. **1**A).

**[0178]** Using the same method just described, two other tissue specific genes—amyloid precursor protein (APP, forward primer, SEQ No. 7; reverse primer, SEQ ID No. 8) found in the brain and associated with Alzheimer's disease, and adenomatous polyposis coli protein (APC) found in the colon and rectum and associated with colorectal cancer (Groden et al. 1991; Santoro and Groden 1997)—were also detected in the RNA extracted from human blood (FIG. **1**B).

## EXAMPLE 6

**[0179]** Multiple RT-PCR Analysis on a Drop of Blood from a Normal/Diseased Individual

**[0180]** A drop of blood was extracted to obtain RNA to carry out quantitative RT-PCR analysis. Specific primers for the insulin gene were designed; forward primer. (5'-GCCCTCTGGGGACCTGAC-3', SEQ ID No. 1) of exon 1 and reverse primer (5'-CCCACCTGCAGGTCCTCT-3", SEQ ID No. 2) of exons 1 and 2 of insulin gene. Such reverse primer was obtained by deleting the intron between the exons 1 and 2. Blood samples of 4 normal subjects were assayed. It was found that the insulin gene is expressed in the blood and the quantitative expression of the insulin gene in a drop of blood is influenced by fasting and non-fasting states of normal healthy subjects (FIG. **2**). This very low level of expression of the insulin gene reflects the phenotypic status of a person and strongly suggests that there is a physiological and pathological role for its expression, contrary to the basal or illegitimate theory of transcription suggested by Chelly et al. (1989) and Kimoto (1998).

**[0181]** Same quantitative RT-PCR analysis was performed using insulin specific primers on RNA samples extracted from a drop of blood from a normal healthy person, a person

having late-onset diabetes (Type II) and a person having asymptomatic diabetes. It was found that the insulin gene is expressed differentially amongst subjects that are healthy, diagnosed as type II diabetic, and also in an asymptomatic preclinical patient (FIG. **3**).

**[0182]** Similarly, specific primers for the atrial natriuretic factor (ANF) gene were designed (forward primer, SEQ ID No. 5; reverse primer, SEQ ID No. 6) and RT-PCR analysis was performed on a drop of blood. ANF is known to be highly expressed in heart tissue biopsies and in the plasma of heart failure patients. However, atrial natriuretic factor was observed to be expressed in the blood and the expression of the atrial natriuretic factor gene is significantly higher in the blood of patients with heart failure as compared to the blood of a normal control patient.

**[0183]** Specific primers for the zinc finger protein gene (ZFP, forward primer, SEQ ID No. 9; reverse primer, SEQ ID No. 10) were also designed and RT-PCR analysis was performed on a drop of blood. ZFP is known to be high in heart tissue biopsies of cardiac hypertrophy and heart failure patients. In the present study, the expression of ZFP was observed in the blood as well as differential expression levels of ZFP amongst the normal, diabetic and asymptomatic preclinical subjects (FIG. **4**); although neither of the non-normal subjects has been specifically diagnosed as suffering from cardiac hypertrophy and/or heart failure, the higher expression levels of the ZFP gene in their blood may indicate that these subjects are headed in that general direction.

**[0184]** It was hypothesized that a housekeeping gene such as glyceraldehyde dehydrogenase (GADH) which is required and highly expressed in all cells would not be differentially expressed in the blood of normal vs. disease subjects. This hypothesis was confirmed by RT-PCR using GADH specific primers (FIG. **4**). Thus, GADH is useful as an internal control.

**[0185]** Standardized levels of insulin gene or ZFP gene expressed in a drop of blood were estimated using a housekeeping gene as an internal control relative to insulin or ZFP expressed (FIGS. **5**A & **5**B). The levels of insulin gene expressed in each fractionated cell from whole blood were also standardized and shown in FIG. **5**C.

## EXAMPLE 7

**[0186]** Human Blood Cell cDNA Library

**[0187]** In order to further substantiate the present invention, differential screening of the human blood cell cDNA library was conducted. cDNA probes derived from human blood, adult heart or brain were respectively hybridized to the human blood cDNA library clones. As shown in FIG. **7**, more than 95% of the "positively" identified clones are identical between the blood and other tissue samples.

**[0188]** DNA sequencing of randomly selected clones from the human whole blood cell cDNA library was also performed. This allowed information regarding the cellular function of blood to be obtained concurrently with gene identification. More than 20,000 expressed sequence tags (ESTs) have been generated and characterized to date, 17.6% of which did not result in a statistically significant match to entries in the GenBank databases and thus were designated as "Novel" ESTs. These results are summarized in FIG. **7** together with the seven cellular functions related to percent distribution of known genes in blood and in the fetal heart.

**[0189]** From 20,000 ESTs, 1,800 have been identified as known genes which may not all appear in the hemapoietic system. For example, the insulin gene and the atrial natriuretic factor gene have not been detected in these 20,000 ESTs but their transcripts were detected in a drop of blood, strongly suggesting that all transcripts of the human genome can be detected by performing RT-PCR analysis on a drop of blood.

**[0190]** In addition, approximately 400 novel genes have been identified from the 20,000 ESTs characterized to date, and these will be subjected to full length sequencing and open reading frame alignment to reduce the actual number of novel ESTs prior to screening for disease markers.

**[0191]** Analysis of the approximately 6,283 ESTs which have known matches in the GenBank databases revealed that this dataset represents over 1,800 unique genes. These genes have been catalogued into seven cellular functions. Comparisons of this set of unique genes with ESTs derived from human brain, heart, lung and kidney demonstrated a greater than 50% overlap in expression (Table 1).

TABLE 1

Overlap of Genes Expressed in Blood *

| Tissues | ESTs** | Overlap in Blood |
|---|---|---|
| brain | 134,000 | 60% |
| heart | 65,000 | 59% |
| lung | 60,200 | 58% |
| kidney | 32,300 | 54% |

* Estimated from limited known genes of about 1,800 as derived from the database of 6,297 ESTs from human blood cell library.
**Obtained from the National Centre of Biotechnology Information (NCBI), U.S.A.

## EXAMPLE 8

Blood Cell ESTs

**[0192]** The results from the differential screening clearly indicate that the transcripts expressed in the whole blood are reflective of genes expressed in all cells and tissues of the body. More than 95% of detectable spots were identical from two different tissues. The remaining 5% of spots may represent cell- or tissue-specific transcripts; however, results obtained from partial sequencing to generate ESTs of these clones revealed most of them not to be cell- or tissue-specific transcripts. Therefore, the negative spots are postulated to be reflective of low abundance transcripts in the tissue from which the cDNA probes were derived.

**[0193]** An alternative approach that was employed to identify transcripts expressed at low levels is the large-scale generation of expressed sequence tags (ESTs). There is substantial evidence regarding the efficiency of this technology to detect previously characterized (known) and uncharacterized (unknown or novel) genes expressed in the cardiovascular system (Hwang & Dempsey et al., 1997). In the present invention, 20,000 ESTs have been produced from a human blood cell cDNA library and resulted in the identification of approximately 1,800 unique known genes (Table 2)

**[0194]** In the most recent GenBank release, analysis of more than 300,000 ESTs in the database (dbESTs) generated more than 48,000 gene clusters which are thought to represent approximately 50% of the genes in the human genome. Only 4,800 of the dbESTS are blood-derived. In the present invention, 20,000 ESTs have been obtained to date from a human blood cDNA library, which provides the world's most informative database with respect to blood cell transcripts. From the limited amount of information generated so far (i.e. 1,800 unique genes), it has already been determined that more than 50% of the transcripts are found in other cells or tissues of the human body (Table 2). Thus, it is expected that by increasing the number of ESTs generated, more genes will be identified that have an overlap in expression between the blood and

other tissues. Furthermore, the transcripts for several genes which are known to have tissue-restricted patterns of expression (i.e. (MyHC, APP, APC, ANF, ZFP) have also been demonstrated to be present in blood.

**[0195]** Most recently, a cDNA library of human hematopoietic progenitor stem cells has also been constructed. From the limited set of 1,000 ESTs, there are at least 200 known genes that are shared with other tissue related genes (Claudio et al. 1998).

**[0196]** Table 2 demonstrates the expression of known genes of specific tissues in blood cells. Previously, only the presence of "housekeeping" genes would have been expected. Additionally, the presence of at least 25 of the currently known 500 genes corresponding to molecular drug targets was detected. These molecular drug targets are used in the treatment of a variety of diseases which involve inflammation, renal and cardiovascular function, neoplastic disease, immunomodulation and viral infection (Drews & Ryser, 1997). It is expected that additional novel ESTs will represent future molecular drug targets.

## EXAMPLE 9

**[0197]** Blood cDNA Chip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Coronary Artery Disease as compared with Gene Expression Profiles from Normal Individuals

**[0198]** A microarray was constructed using cDNA clones from a human peripheral blood cell cDNA library, as described herein. A total of 10,368 polymerase chain reaction (PCR) products of the clones from the human peripheral blood cell cDNA library were arrayed using GNS 417 arrpyer (Affymetrix). RNA for microarray analysis was isolated from whole block samples obtained from three male and one female patients with coronary heart disease (80-90% stenosis) receiving vascular extension drugs and awaiting bypass surgery, and three healthy male controls.

**[0199]** A method of high-fidelity mRNA amplification from 1 pg of total RNA sample was used. Cy5- or Cy3-dUTP was incorporated into cDNA probes by reverse transcription of anti-sense RNA, primed by oligo-dT. Labeled probes were purified and concentrated to the desired volume. Pre-hybridization and hybridization were performed following Hegde's protocol (Hegde P et al. A concise guide to cDNA microarray analysis. Biotechniques 2000,29, 548-56). After overnight hybridization and washing, hybridization signals were detected with a GMS 418 scanner at 635-nm (Cy5) and 532-nm (Cy3) wave lengths (see FIG. **24**). Two RNA pools were labeled alternatively with Cy5- and Cy3-dUTP, and each experiment was repeated twice. Cluster analysis using GeneSpring 4.1.5 (Silicon Genetics) revealed two distinct groups consisting of four CAD and three normal control samples. Two images scanned at different wavelengths were superimposed. Individual spots were identified on a customized grid. Of 10,368 spots, 10,012 (96.6%) were selected after the removal of spots with irregular shapes. Data quality was assessed with values of Ch1GTB2 and Ch2GTB2 provided by ScanAlyze. Only spots with Ch1GTB2 and Ch2GTB2 over 0.50 were selected. After evaluation of signal intensities, 8750 (84.4%) spots were left. Signal intensities were normalized using a scatter-plot of the signal intensities of the two channels. After normalization, the expression ratios of β-actin were 1.00+0.21 1.11+0.22, 1.14+0.20 and 1.30+0.18 (24 samples of β-actin were spotted on this slide as the positive control) in the four images. Gene differential expression was assessed as the ratio of two wave-length signal intensities. Spots showing a differential expression more than two-fold in all four experiments were identified as peripheral blood cell, differentially expressed candidate genes in CAD. 108. genes are differentially expressed in CAD peripheral blood cells, 43 genes are downregulated in CAD blood cells and 65 are upregulated (see Table 5). Functional characterization of these genes shows that differential expression takes place in every gene functional category, indicating that, profound changes occur in CAD blood cells.

**[0200]** The differential expression of three genes, proplatelet basic protein (PBP), platelet factor 4 (PF4) and coagulation factor XIII A1 (F13A), initially identified in the microarray data analysis, was further examined by reverse transcriptase-PCR (RT-PCR) using the Titan One-tube RT-PCR kit (Boehringer Mannheim). Reaction solution contains 0.2 mM each dNTP, 5 mM DTT, 1.5 mM MgCl 0.1 pg of total RNA from each sample and 20 pmol each of left and right primers of PBP (5'-GGTGCTGCTGCTTCTGTCAT-3' and 5'-GGCAGATTTTCCTCCCATCC-3'), F13A (5CAGTCCACCGTGCTAACCATC-3' and 5'-AGGGAGTCACTGCTCATGCT-3') and PF4 (5' GTTGCTGCTCCTGCCACTT 3' and 5' GTGGCTATCAGTTGGGCAGT-3'). RT-PCR steps are as follows: 1. reverse-transcription: 30 min at 60° C.; 2. PCR: 2 min at 94° C., followed by 30-35 cycles (as optimized for each gene) for 30 s at 94° C., 30 s at optimized annealing temperature and 2 min at 68° C.; 3. final extension: 7 min at 68° C. PCR, products were electrophoresed on 1.5% agarose gels. Human (β-actin primers (5'-GCGAGAAGATGACCCAGATCAT-3' and 5'-GCTCAGGAGGAGCAATGATCTT-3') were used as the internal control. The RT-PCR analysis confirmed that the expression of the three secreted proteins: PBP, PF4 and F13A were all unregulated in CAD blood cells (see FIG. **23**).

TABLE 5

| | Accession number | Fold (average) | Functional category | Protein Accession Number |
|---|---|---|---|---|
| Upregulated gene in CAD | | | | |
| REV3-like, catalytic subunit of DNA polymerase zeta | AF035537 | 2.3 | Cell cycle | NP_002903 |
| TGFB1-induced anti-apoptotic factor 1 | D86970 | 2.2 | Cell cycle | NP_510880 |
| A disintegrin and metalloproteinase domain 10 | AA044656 | 2.7 | Cell signaling | NP_001101 |
| Centaurin, delta 2 | AA351412 | 2 | Cell signaling | NP_631920 |
| Chloride intracellular channel 4 | AA411940 | 2.2 | Cell signaling | NP_039234 |
| Endothelin receptor typeA | D90348 | 2.1 | Cell signaling | NP_001948 |
| Glutamate receptor, ionotropic | N33821 | 2.4 | Cell signaling | NP_777567 |
| Mitogen-activated protein kinase 7 | L38486 | 3.7 | Cell signaling | NP_002395 |

TABLE 5-continued

| | Accession number | Fold (average) | Functional category | Protein Accession Number |
|---|---|---|---|---|
| Mitogen-activated protein kinase kinase kinase 7 | AB009356 | 4.5 | Cell signaling | NP_663306 |
| Myristoylated alanine-rich protein kinase C substrate | D10522 | 2.5 | Cell signaling | NP_002347 |
| NIMA-related kinase 7 | AA093324 | 3.5 | Cell signaling | NP_598001 |
| PAK2 | AA262968 | 3.5 | Cell signaling | Q13177 |
| Phospholipid scrambiase 1 | AA054476 | 3.3 | Cell signaling | NP_066928 |
| Serum deprivation response | Z30112 | 4.5 | Cell signaling | NP_004648 |
| Adducin 3 | AA029158 | 2.9 | Cell structure | NP_063968 |
| Desmin | AF167579 | 4.4 | Cell structure | NP_001918 |
| Fibromodulin | W23613 | 2.9 | Cell structure | NP_002014 |
| Laminin, beta 2 | S77512 | 2.2 | Cell structure | NP_002283 |
| Laminin, beta 3 | L25541 | 2.4 | Cell structure | NP_000219 |
| Osteonectin | Y00755 | 3.1 | Cell structure | NP_003109 |
| CD59 antigen p18-20 | W01111 | 2.4 | Cell/organism defense | NP_000602 |
| Clusterin | M64722 | 3.5 | Cell/organism defense | NP_001822 |
| F13A | M14539 | 2.1 | Cell/organism detense | NP_000120 |
| Defensin, alpha 1 | M26602 | 4.2 | Cell/organism defense | NP_004075 |
| PF4 | M25897 | 2.1 | Cell/organism defense | NP_002610 |
| PBP | M54995 | 5.5 | Cell/organism defense | NP_002695 |
| E2F transcription factor 3 | D38550 | 2.1 | Gene expression | NP_001940 |
| Early growth response 1 | M62829 | 2.7 | Gene expression | NP_001955 |
| Eukaryotic translation elongation factor 1 alpha 1 | N86030 | 2.3 | Gene expression | NP_001393 |
| Eukaryotic translation initiation factor 4E | M15353 | 2.1 | Gene expression | NP_001959 |
| F-box and WD-40 domain protein 1B | AB014596 | 2.7 | Gene expression | NP_387449 |
| Makorin, ring finger protein, 2 | AA331966 | 2.1 | Gene expression | NP_054879 |
| Non-canonical ubiquitin-conjugating enzyme 1 | N92776 | 2.5 | Gene expression | NP_057420 |
| Nuclear receptor subfamily 1, group l, member 3 | Z30425 | 4.7 | Gene expression | NP_005113 |
| Ring finger protein 11 | T08927 | 3 | Gene expression | NP_055187 |
| Transducin-like enhancer of split 1 | M99435 | 3.3 | Gene expression | NP_005068 |
| Alkaline phosphatase, liver/bone/kidney | AB011406 | 2.2 | Metabolism | NP_000469 |
| Annexin A3 | M63310 | 3.4 | Metabolism | NP_005130 |
| Branched chain aminotransferase 1, cytosolic | AA336265 | 4.8 | Metabolism | NP_005495.1 |
| Cytochrome b | AF042500 | 2.5 | Metabolism | |
| Glutaminase | D30931 | 2.6 | Metabolism | NP_055720 |
| Lysophospholipase | AF035293 | 2.8 | Metabolism | NP_006321 |
| NADH dehydrogenase 1, subcomplex unknown 1, 6 kDa | AA056111 | 2.5 | Metabolism | NP_002485 |
| Phosphofructokinase | M26066 | 2.2 | Metabolism | NP_000280 |
| Ubiquinol-cytochrome c reductase binding protein | M22348 | 2.5 | Metabolism | NP_006285 |
| CGl-110 protein | AA341061 | 2.4 | Unclassified | NP_057131 |
| Dactylidin | H95397 | 2.7 | Unclassified | NP_112225 |
| Deleted in split-hand/split-foot 1 region | T24503 | 2.4 | Unclassified | NP_006295 |
| Follistatin-like 1 | R14219 | 2.7 | Unclassified | NP_009016 |
| FUS-interacting protein 1 | W37945 | 2.8 | Unclassified | NP_473357 |
| Hypothetical protein FLJ12619 | W47233 | 7 | Unclassified | NP_112201 |
| Hypothetical protein from EUROIMAGE 588495 | N68247 | 2.7 | Unclassified | |
| Hypothetical protein LOC51315 | AA251423 | 2.2 | Unclassified | NP_057702 |
| KIAA1705 protein | T80569 | 2.7 | Unclassified | NP_009121.1 |
| Mesoderm induction early response 1 | AI650409 | 2.2 | Unclassified | NP_065999 |
| Phosphodiesterase 4D-interacting protein | AA740661 | 2.5 | Unclassified | NP_055459 |
| Preimplantation protein 3 | D59087 | 2.5 | Unclassified | NP_056202 |
| Putative nuclear protein ORF1-FL49 | W33098 | 2.8 | Unclassified | NP_115788 |
| Similar to rat nuclear ubiquitous casein kinase 2 | H09434 | 2.2 | Unclassified | Q9H1E3 |
| Similar to RIKEN | AA297412 | 2.5 | Unclassified | T02670 |
| Spectrin, beta | A1334431 | 2.5 | Unclassified | Q01082 |
| Stromal cell-derived factor receptor 1 | H71558 | 4.1 | Unclassified | NP_816929 |
| Thioredoxin-related protein | AA421549 | 2.8 | Unclassified | NP_110437 |
| Transmembrane 4 superfamily member 2 | D29808 | 2.4 | Unclassified | NP_004606 |
| Tumor endothelial marker 8 | D79964 | 2.5 | Unclassified | NP_444262 |
| Downregulated gene in CAD | | | | |
| CASP8 and FADD-like apoptosis regulator | AF015450 | 0.45 | Cell cycle | NP_003870 |

TABLE 5-continued

| | Accession number | Fold (average) | Functional category | Protein Accession Number |
|---|---|---|---|---|
| CD81 antigen | M33680 | 0.41 | Cell cycle | NP_004347 |
| Cell division cycle 25B | M81934 | 0.4 | Cell cycle | MP_088860 |
| DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 27 | AA985699 | 0.42 | Cell cycle | NP_694705 |
| F-box and leucine-rich repeat protein 11 | R98291 | 0.27 | Cell cycle | NP_036440 |
| Minichromosome maintenance deficient 3 associated protein | H10286 | 0.43 | Cell cycle | NP_003897 |
| Protein phosphatase 2, regulatory subunit A, alpha isoform | J02902 | 0.48 | Cell cycle | NP_055040 |
| Thyroid autoantigen 70 kDa | J04607 | 0.25 | Cell cycle | NP_001460 |
| A disintegrin and metalloproteinase domain 17 | R32760 | 0.37 | Cell signaling | |
| A kinase anchor protein 13 | M90360 | 0.31 | Cell signaling | NP_658913 |
| Calpastatin | AF037194 | 0.39 | Cell signaling | NP_006471 |
| Diacylglycerol kinase, alpha 80 kDa | AF064770 | 0.44 | Cell signaling | NP_001336 |
| gamma-aminobutyric acid B receptor, 1 | AJ012187 | 0.42 | Cell signaling | NP_068705 |
| Inositol polyphosphate-5-phosphatase, 145 kDa | U84400 | 0.41 | Cell signaling | NP_005532 |
| Lymphocyte-specific protein tyrosine kinase | X05027 | 0.45 | Cell signaling | NP_005347 |
| RAP1B, member of RAS oncogene family | P09526 | 0.4 | Cell signaling | P09526 |
| Ras association (RalGDS/AF-6) domain family 1 | AF061836 | 0.43 | Cell signaling | NP_733835 |
| CDC42-effector protein 3 | AF104857 | 0.28 | Cell signaling | NP_006440 |
| Leupaxin | AF062075 | 0.31 | Cell signaling | NP_004802 |
| Annexin A6 | D00510 | 0.45 | Cell structure | NP_004024 |
| RAN-binding protein 9 | AB008515 | 0.41 | Cell structure | NP_005484 |
| Thymosin, beta 10 | M20259 | 0.26 | Cell structure | NP_066926 |
| GranzymeA | M18737 | 0.17 | Cell/organism defense | NP_006135 |
| ThromboxaneA synthase 1 | M80646 | 0.44 | Cell/organism defense | NP_112246 |
| Coatomer protein complex, subunit beta | AA357332 | 0.39 | Gene expression | NP_057535 |
| Cold-inducible RNA-binding protein | H39820 | 0.27 | Gene expression | NP_001271 |
| Leucine-rich repeat interacting protein 1 | U69609 | 0.44 | Gene expression | NP_004726 |
| Proteasome subunit, alpha type, 3 | D00762 | 0.31 | Gene expression | NP_687033 |
| Proteasome subunit, alpha type, 7 | AF022815 | 0.35 | Gene expression | NP_689468 |
| Protein phosphatase 1G, gamma isoform | AI417405 | 0.5 | Gene expression | NP_817092 |
| Ribonuclease/angiogenin inhibitor | M36717 | 0.44 | Gene expression | NP_002930 |
| RNA-binding protein-regulatory subunit | AF021819 | 0.3 | Gene expression | NP_009193 |
| Signal transducer and activator of transcription 6 | U16031 | 0.45 | Gene expression | NP_003144 |
| Transcription factor A, mitochondrial | M62810 | 0.41 | Gene expression | NP_036383 |
| Ubiquitin-specific protease 4 | AF017306 | 0.31 | Gene expression | NP_003354 |
| Dehydrogenase/reductase SDR famiy member 1 | AA100046 | 0.46 | Metabolism | NP_612461 |
| Solute carrier family 25, member 6 | J03592 | 0.3 | Metabolism | NP_001627 |
| Amplified in osteosarcoma | U41635 | 0.45 | Unclassified | NP_006803 |
| Expressed in activated T/LAK lymphocytes | C00577 | 0.45 | Unclassified | NP_009198 |
| Integral inner nuclear membrane protein | W00460 | 0.4 | Unclassified | NP_055134 |
| Phosphodiesterase 4D-interacting protein | T95969 | 0.45 | Unclassified | NP_055459 |
| Tumor endothelial marker 7 precursor | N93789 | 0.45 | Unclassified | NP_065138 |
| Wiskott-Aldrich syndrome protein interacting protein | AF031588 | 0.22 | Unclassified | NP_003378 |

## EXAMPLE 10

**[0201]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Osteoarthritis and Hypertension as Compared with Gene Expression Profiles from Normal Individuals

**[0202]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with osteoarthritis and hypertension on as compared to blood samples taken from healthy patients.

**[0203]** As used herein, the term "hypertension" is defined as high blood pressure or elevated arterial pressure. Patients identified with hypertension herein include persons who have an increased risk of developing a morbid cardiovascular event and/or persons who benefit from medical therapy designer to treat hypertension. Patients identified with hypertension also can include persons having systolic blood pressure of >130 mm Hg or a diastolic blood pressure of >90 mm Hg or a person takes antihypertensive medication.

**[0204]** Osteoarthritis (OA), as used herein also known as "degenerative joint disease", represents failure of a diarthrodial (movable, synovial-lined) joint. It is a condition, which affects joint cartilage, and or subsequently underlying bone and supporting tissues leading to pain, stiffness, movement

problems and activity limitations. It most often affects the hip, knee, foot, and hand, but can affect other joints as well.

**[0205]** OA severity can be graded according to the system described by Marshall (Marshall K W. J Rheumatol, 1996:23 (4) 582-85). Briefly, each of the six knee articular surfaces was assigned a cartilage grade with points based on the worst lesion seen on each particular surface. Grade 0 is normal (0 points), grade 1 cartilage is soft or swollen but the articular surface is intact (1 point). In Grade II lesions, the cartilage surface is not intact but the lesion does not extend down to subchondral bone (2 points). Grade III damage extends to subchondral bone but the bone is neither eroded nor eburnated (3 points). In Grade IV lesions, there is eburnation of or erosion into bone (4 points). A global OA score is calculated by summing the points from all six cartilage surfaces. If there is any associated pathology, such as meniscus tear, an extra point will be added to the global score. Based on the total score, each patient is then categorized into one of four OA groups: mild (1-6), moderate (7-12), marked (13-18), and severe (>18). As used herein, patients identified with OA may be categorized in any of the four OA groupings as described above.

**[0206]** Blood samples were taken from patients who were diagnosed with osteoarthritis and hypertension as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of osteoarthritis and hypertension was corroborated by a skilled Board certified physician.

**[0207]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with disease as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0208]** FIG. **8** shows a diagrammatic representation of gene expression profiles of blood samples from individuals having hypertension as compared with gene expression profiles from normal individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. In this example, hypertensive patients also presented with OA, as described herein. Normal individuals have no known medical conditions and were not taking any known medication. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who are hypertensive or normal. The "*" indicates those patients who abnormally clustered as either hypertensive, or normal despite presenting with the reverse. The number of hybridizations profiles determined for either hypertensive patients or normal individuals are shown. 861 differentially expressed genes were identified as being differentially expressed with a p value of $<0.05$ as between the hypertensive patients and normal individuals. The identity of the differentially expressed genes is shown in Table 3A.

## EXAMPLE 11

**[0209]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Osteoarthritis and Obesity as Compared with Gene Expression Profiles from Normal Individuals.

**[0210]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with obesity as compared to blood samples taken from healthy patients.

**[0211]** As used herein, "obesity" is defined as an excess of adipose tissue that imparts a health risk. Obesity is assessed in terms of height and weight in the relevance of age. Patients who are considered obese include, but are not limited to, patients having a body mass index or BMI ((defined as body weight in kg divided by (height in meters)$^2$) greater than or equal to 30.0. Patients having obesity as defined herein are those with a BMI of greater than or equal to 30.0.

**[0212]** Blood samples were taken from patients who were diagnosed with osteoarthritis and obesity as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of the disease was corroborated by a skilled Board certified physician. Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (ChondroChip) as described herein. Identification of genes differentially expressed in blood samples from patients with disease as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0213]** FIG. **9** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as obese as described herein as compared with gene expression profiles from normal individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. In this example, obese patients also presented with OA, as described herein. Normal individuals have no known medical conditions and were not taking any known medication. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who are obese or normal. The "*" indicates those patients who abnormally clustered as either obese or normal despite presenting with the reverse. The number of hybridization profiles determined for obese patients and normal individuals are shown. 913 genes were identified as being differentially expressed with a p value of $<0.05$ as between the obese patients and normal individuals is noted. The identity of the differentially expressed genes is shown in Table 3B.

## EXAMPLE 12

**[0214]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Osteoarthritis and Allergies as Compared with Gene Expression Profiles from Normal Individuals

**[0215]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with allergies as compared to blood samples taken from healthy patients.

**[0216]** As used herein, "allergies" encompasses diseases and conditions wherein a patient demonstrates a hypersensi-

tive or allergic reaction to one or more substances or stimuli such as drugs, food stuffs, plants, animals etc. and as a result has an increased immune response. Such immune responses can include anaphylaxis, allergic rhinitis, asthma, skin sensitivity such as urticaria, eczema, and allergic contact dermatitis and ocular allergies such as allergic conjunctivitis and contact allergy. Patients identified as having allergies includes patients having one or more of the above noted conditions.

**[0217]** Blood samples were taken from patients who were diagnosed with osteoarthritis and allergies as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of osteoarthritis and allergies was corroborated by a skilled Board certified physician.

**[0218]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with osteoarthritis and allergies as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0219]** FIG. **10** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having allergies as described herein as compared with gene expression profiles from normal individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. In this example, patients with allergies also presented with OA, as described herein. Normal individuals have no known medical conditions and were not taking any known medication. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who are obese or normal. The "*" indicates those patients who abnormally clustered as either having allergies or being normal despite presenting with the reverse. The number of hybridizations profiles determined for patients with allergies and normal individuals are shown. 633 genes were identified as being differentially expressed with a p value of <0.05 as between patients with allergies and normal individuals is noted. The identity of the differentially expressed genes is shown in Table 3C.

## EXAMPLE 13

**[0220]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Osteoarthritis and Subject to Systemic Steroids as Compared with Gene Expression Profiles from Normal Individuals

**[0221]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients subject to systemic steroids as compared to blood samples taken from healthy patients.

**[0222]** As used herein, "systemic steroids" indicates a person subjected to artificial levels of steroids as a result of medical intervention. Such systemic steroids include birth control pills, prednisone, and hormones as a result of hormone replacement treatment. A person identified as having systemic steroids is one who is on one or more of the following treatment regimes.

**[0223]** Blood samples were taken from patients who were diagnosed with osteoarthritis and subject to systemic steroids as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of osteoarthritis and systemic steroids was corroborated by a skilled Board certified physician.

**[0224]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to the 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with osteoarthritis and subject to systemic steroids as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0225]** FIG. **11** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were subject to systemic steroids as described herein as compared with gene expression profiles from normal individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. In this example, patients taking systemic steroids also presented with OA, as described herein. Normal individuals have no known medical conditions and were not taking any known medication. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who are taking systemic steroids or normal. The "*" indicates those patients who abnormally clustered as either systemic steroids or normal despite presenting with the reverse. The number of hybridizations profiles determined for patients with systemic steroids and normal individuals are shown. 605 genes were identified as being differentially expressed with a p value of <0.05 as between patients with systemic steroids and normal individuals is noted. The identity of the differentially expressed genes is shown in Table 3D.

## EXAMPLE 14

**[0226]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Hypertension as Compared with Gene Expression Profiles from Normal Individuals

**[0227]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with hypertension but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0228]** As used herein, the term "hypertension" is defined as high blood pressure or elevated arterial pressure. Patients identified with hypertension herein include persons who have an increased risk of developing a morbid cardiovascular event and/or persons who benefit from medical therapy designed to treat hypertension. Patients identified with hypertension also can include persons having systolic blood pressure of >130

mm Hg or a diastolic blood pressure of >90 mm Hg or a person takes antihypertensive medication.

**[0229]** Blood samples were taken from patients who were diagnosed with hypertension as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of hypertension was corroborated by a skilled Board certified physician.

**[0230]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (ChondroChip) as described herein. Identification of genes differentially expressed in blood samples from patients with hypertension as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A, Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0231]** FIG. **12** shows a diagrammatic representation of gene expression profiles of blood samples from individuals having hypertension as compared with gene expression profiles from samples of both non-hypertensive and normal individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Non-hypertensive individuals presented without hypertension, but may have presented with other medical conditions and may be under various treatment regimes. Normal individuals have no known medical conditions and were not taking any known medication. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who are hypertensive, normal or non-hypertensive. The "*" indicates those patients who abnormally clustered as either hypertensive, non-hypertensive or normal despite actual presentation. The number of hybridizations profiles determined for hypertensive patients, non-hypertensive patients and normal individuals are shown. 1,993 genes identified as being differentially expressed with a p value of $<0.05$ as between the hypertensive patients and the combined normal and non-hypertensive individuals is noted. The identity of the differentially expressed genes are shown in Table 3E.

## EXAMPLE 15

**[0232]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Obesity as Compared with Gene Expression Profiles from Normal Individuals

**[0233]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with obesity but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0234]** As used herein, "obesity" is defined as an excess of adipose tissue that imparts a health risk. Obesity, is assessed in terms of height and weight in the relevance of age. Patients who are considered obese include, but are not limited to, patients having a body mass index or BMI ((defined as body weight in kg divided by (height in meters)$^2$) greater than or equal to 30.0. Patients having obesity as defined herein are those without BMI of greater than or equal to 30.0.

**[0235]** Blood samples were taken from patients who were diagnosed with hypertension as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of obesity was corroborated by a skilled Board certified physician.

**[0236]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent. (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with obesity as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0237]** FIG. **13** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as obese as described herein as compared with gene expression profiles from normal and non-obese individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non-obese individuals presented without obesity, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who are obese, normal or non-obese. The "*" indicates those patients who abnormally clustered as either obese, normal or non-obese despite actual presentation. The number of hybridizations profiles determined for obese patients, non-obese patients and normal individuals are shown. 1,147 genes were identified as being differentially expressed with a p value of $<0.05$ as between the obese patients and the combination of normal and non-obese individuals is noted. The identity of the differentially expressed genes is shown in Table 3F.

## EXAMPLE 16

**[0238]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Type 2 Diabetes as Compared with Gene Expression Profiles from Normal Individuals

**[0239]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with type 2 diabetes but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0240]** As used herein, "diabetes", or "diabetes mellitus" includes both "type 1 diabetes" (insulin-dependent diabetes (IDDM)) and "type 2 diabetes" (insulin-independent diabetes (NIDDM). Both type 1 and type 2 diabetes characterized in accordance with Harrison's Principles of Internal Medicine 14th edition, as a person having a venous plasma glucose concentration $\geqq$140 mg/dL on at least two separate occasions after overnight fasting and venous plasma glucose concentration $\geqq$200 mg/dL at 2 h and on at least one other occasion during the 2-h test following ingestion of 75 g of glucose. Patients identified as having type 2 diabetes as described

herein are those demonstrating insulin-independent diabetes as determined by the methods described above.

**[0241]** Blood samples were taken from patients who were diagnosed with type II diabetes as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of type II diabetes was corroborated by a skilled Board certified physician.

**[0242]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with type diabetes as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0243]** FIG. **14** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having type 2 diabetes as described herein as compared with gene expression profiles from normal and non-type 2 diabetes individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non-type 2 diabetes individuals presented without type 2 diabetes, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have type 2 diabetes, are normal or do not have type 2 diabetes. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for type 2 diabetes, non-type 2 diabetes and normal individuals are shown. 915 were identified as being differentially expressed with a p value of <0.05 as between the type 2 diabetes patients and the combination of normal and non type 2 diabetes individuals is noted. The identity of the differentially expressed genes is shown in Table 3G.

## EXAMPLE 17

**[0244]** Chondrochip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having hyperlipidemia as Compared with Gene Expression Profiles from Normal Individuals

**[0245]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with hyperlipidemia but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0246]** As used herein, "hyperlipidemia" is defined as an elevation of lipid protein profiles and includes the elevation of chylomicrons, very low-density lipeproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and/or high-density lipoproteins (HDL) as compared with the general population. Hyperlipidemia includes hypercholesterolemia and/or hypertriglyceridemia. By hypercholesterolemia, it is meantelevated fasting plasma total cholesterol level of >200 mg/dL, and/or LDL-cholesterol levels of >130 mg/dL. A desirable level of HDL-cholesterol is >60 mg/dL. By hypertriglyceridemia it is meant plasma triglyceride (TG) concentrations of greater than the $90^{th}$ or $95^{th}$ percentile for age and sex and can include, for example, TG>160 mg/dL as determined after an overnight fast.

**[0247]** Blood samples were taken from patients who were diagnosed with hyperlipidemia as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of hyperlipidemia was corroborated by a skilled Board certified physician.

**[0248]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with hyperlipidemia as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0249]** FIG. **15** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having hyperlipidemia as described herein as compared with gene expression profiles from normal and non-hyperlipidemia patients. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non hyperlipidemia individuals presented without elevated cholesterol or elevated triglycerides but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the ChondroChip (version2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have elevated lipids and/or cholesterol, are normal or do not have elevated lipids or cholesterol. The "*" indicates those patients who abnormally clustered as having either hyperlipidemia, normal or non-hyperlipidemia despite actual presentation. The number of hybridizations profiles determined for hyperlipidemia patients, non-hyperlipidemia patients and normal individuals are shown. 1,022 genes were identified as being differentially expressed with a p value of <0.05 as between the patients with hyperlipidemia and the combination of normal and non hyperlipidemia individuals. The identity of the differentially expressed genes is shown in Table 3H.

## EXAMPLE 18

**[0250]** Chondrochip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Lung Disease as Compared with Gene Expression Profiles from Normal Individuals

**[0251]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with lung disease but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0252]** As used herein, "lung disease" encompasses any disease that affects the respiratory system and includes bronchitis, chronic obstructive lung disease, emphysema, asthma, lung cancer. Patients identified as having lung disease includes patients having one or more of the above noted conditions.

**[0253]** Blood samples were taken from patients who were diagnosed with lung disease as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of lung disease was corroborated by a skilled Board certified physician.

**[0254]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with lung disease as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0255]** FIG. **16** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having lung disease as described herein as compared with gene expression profiles from normal and non lung disease individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non-lung disease individuals presented without lung disease, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have lung disease, are normal or do not have lung disease. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for either the lung disease patients, non-lung disease patients and normal individuals are show. 596 genes were identified as being differentially expressed with a p value of <0.05 as between the lung disease patients and the combination of normal and non lung disease individuals is noted. The identity of the differentially expressed genes is shown in Table 3I.

## EXAMPLE 19

**[0256]** Affymetrix U133A Chip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Bladder Cancer as Compared with Gene Expression Profiles from Normal Individuals

**[0257]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with bladder cancer but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0258]** As used herein, the term "cancer" or "carcinoma" is defined as a disease in, which cells behave abnormally and includes; (i) cancers which originate from a single cell proliferating to form a clone of malignant cells, (ii) cancers wherein the growth of the cell is not regulated by normal biological and physical influences of the environment, (iii) anaplasic cancer, wherein the cells lack normal coordinated cell differentiation and (iv) metastasis cancer, wherein the cells have the capacity for discontinuous growth and dissemination to other parts of the body. The diagnosis of cancer can include careful clinical assessment and/or diagnostic investigations including endoscopy, imaging, histopathology, cytology and laboratory studies.

**[0259]** As used herein, "bladder cancer" includes carcinomas that occur in the transitional epithelium lining the urinary tract, starting at the renal pelvis and extending through the ureter, the urinary bladder, and the proximal two-thirds of the urethra. As used herein, patients diagnosed with bladder cancer include patients diagnosed utilizing any of the following methods or a combination thereof: urinary cytologic evaluation, endoscopic evaluation for the presence of malignant cells, CT (computed tomography), MRI (magnetic resonance imaging) for metastasis status.

**[0260]** Blood samples were taken from patients who were diagnosed with bladder cancer as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of bladder cancer was corroborated by a skilled Board certified physician.

**[0261]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a Affymetrix U133A Chip as described herein. Identification of genes differentially expressed in blood samples from patients with bladder cancer as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0262]** FIG. **17** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having bladder cancer as described herein as compared with gene expression profiles from non bladder cancer individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Non bladder cancer individuals presented without bladder cancer, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the Affymetrix U1338 chip. A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have bladder cancer, or do not have bladder cancer. The "*" indicates those patients who abnormally clustered as either bladder cancer, or non bladder cancer despite actual presentation. The number of hybridizations profiles determined for patients with bladder cancer and without bladder cancer are shown. 4,228 genes were identified as being differentially expressed with a p value of <0.05 as between the bladder cancer patients and the non bladder cancer individuals is noted. The identity of the differentially expressed genes is shown in Table 3J.

## EXAMPLE 20

**[0263]** Affymetrix U133A Chip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individu-

als having Early or Advanced Bladder Cancer as Compared with Gene Expression Profiles from Normal Individuals

**[0264]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with early or advanced late stage bladder cancer but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0265]** As used herein, "early stage bladder cancer" includes bladder cancer wherein the detection of the anatomic extent of the tumor, both in its primary location and in metastatic sites, as defined by the TNM staging system in accordance with Harrison's Principles of Internal Medicine 14th edition can be considered early stage. More specifically, early stage bladder cancer can include those instances wherein the carcinoma is mainly superficial.

**[0266]** As used herein, "advanced stage bladder cancer" is defined as bladder cancer wherein the detection of the anatomic extent of the tumor, both in its primary location and in metastatic sites, as defined by the TNM staging system in accordance with Harrison's Principles of Internal Medicine 14th edition, can be considered as advanced stage. More specifically, advanced stage carcinomas can involve instances wherein the cancer has infiltrated the muscle and wherein metastasis has occurred.

**[0267]** Blood samples were taken from patients who were diagnosed with early or advanced late stage bladder cancer as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of early or advanced late stage bladder cancer was corroborated by a skilled Board certified physician.

**[0268]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a Affymetrix U133A Chip as described herein. Identification of genes differentially expressed in blood samples from patients with early or advanced late stage bladder cancer as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York; USA: McGraw-Hill Medical Publishing Division, 2002).

**[0269]** FIG. **18** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having advanced stage bladder cancer or early stage bladder cancer as described herein as compared with gene expression profiles from non bladder cancer,individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Non bladder cancer individuals presented without bladder cancer, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the Affymetrix U1338 chip. A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have early stage bladder cancer, advanced stage bladder cancer, or do not have bladder cancer. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for either early stage bladder cancer, advanced bladder cancer or non-bladder cancer are shown. 3,518 genes were identified as being differentially expressed with a p value of $<0.05$ as between the bladder cancer patients and the non bladder cancer individuals is noted. The identity of the differentially expressed genes is shown in Table 3K.

## EXAMPLE 21

**[0270]** Affymetrix U133A Chip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Coronary Artery Disease as Compared with Gene Expression Profiles from Normal Individuals

**[0271]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with coronary artery disease but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0272]** As used herein, "Coronary artery disease" (CAD) is defined as a condition wherein at least one coronary artery has >50% luminal diameter stenosis, as diagnosed by coronary angiography and includes conditions in which there is atheromatous narrowing and subsequent occlusion of the vessel. CAD includes those conditions which manifest as angina, silent ischaemia, unstable angina, myocardial infarction, arrhythmias, heart failure, and sudden death. Patients identified as having CAD herein Coronary artery disease is defined

**[0273]** Blood samples were taken from patients who were diagnosed with Coronary artery disease as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of Coronary artery disease was corroborated by a skilled Board certified physician.

**[0274]** Total mRNA from a drop of peripheral whole blond taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a Affymetrix U133A Chip as described herein. Identification of genes differentially expressed in blood samples from patients with Coronary artery disease as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0275]** FIG. **19** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having coronary artery disease (CAD) as described herein as compared with gene expression profiles from non-coronary artery disease individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Non coronary artery disease individuals presented without coronary artery disease, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using the Affymetrix™ U1338 chip. A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have coronary artery disease or do not have coronary artery disease. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for patients with CAD or without CAD are shown. 967 genes were identified as being differentially expressed with a p value of $<0.05$ as between the coronary artery disease patients

and those individuals without coronary artery disease is noted. The identity of the differentially expressed genes is shown in Table 3L.

EXAMPLE 22

**[0276]** Affymetrix U133A Chip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Rheumatoid Arthritis as Compared with Gene Expression Profiles from Normal Individuals

**[0277]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with Rheumatoid arthritis but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0278]** Rheumatoid arthritis (RA) is defined as a chronic, multisystem disease of unknown etiology with the characteristic feature of persistent inflammatory synovitis. Said inflammatory synovitis usually involves peripheral joints in a systemic distribution. Patients having RA as defined herein were identified as having one or more of the following; (i) cartilage destruction, (ii) bone erosions and/or-(iii) joint deformities.

**[0279]** Blood samples were taken from patients who were diagnosed Rheumatoid arthritis as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of Rheumatoid arthritis was corroborated by a skilled Board certified physician.

**[0280]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a Affymetrix U133A Chip as described herein. Identification of genes differentially expressed in blood samples from patients with Rheumatoid arthritis as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0281]** FIG. **20** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having rheumatoid arthritis as described herein as compared with gene expression profiles from non-rheumatoid arthritis individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non rheumatoid arthritis individuals presented without rheumatoid arthritis, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using ChondroChip (version2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have rheumatoid arthritis or do not have rheumatoid arthritis. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for patients with rheumatoid arthritis and without rheumatoid arthritis are shown. 2,068 genes were identified as being differentially expressed with a p value of $<0.05$ as between the rheumatoid arthritis patients and a combination of those individuals without rheumatoid arthritis and normal is noted. The identity of the differentially expressed genes is shown in Table 3M.

EXAMPLE 23

**[0282]** Affymetrix U133A Chip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Depression as Compared with Gene Expression Profiles from Normal Individuals

**[0283]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with depression but without osteoarthritis as compared to blood samples taken from healthy patients.

**[0284]** As used herein "mood disorders" are conditions characterized by a disturbance in the regulation of mood, behaviour, and affect. "Mood disorders" can include depression, anxiety, schizophrenia, bipolar disorder, manic depression and the like.

**[0285]** As used herein "depression" includes depressive disorders or depression in association with medical illness or substance abuse in addition to depression as a result of sociological situations. Patients defined as having depression were diagnosed mainly on the basis of clinical symptoms including a depressed mood episode wherein a person displays a depressed mood on a daily basis for a period of greater than 2 weeks. A depressed mood episode may be characterized by sadness, indifference, apathy, or irritability and is usually associated with changes in a number of neurovegetative functions, including sleep patterns, appetite and weight, fatigue, impairment in concentration and decision making.

**[0286]** Blood samples were taken from patients who were diagnosed with depression as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of depression was corroborated by a skilled Board certified physician.

**[0287]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a Affymetrix U133A Chip as described herein. Identification of genes differentially expressed in blood samples from patients with depression as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0288]** FIG. **21** shows a diagrammatic representation of gene expression profiles of blood samples from individuals who were identified as having depression as described herein as compared with gene expression profiles from non-depression individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Non depression individuals presented without depression, but may have presented with other medical conditions and may be under various treatment regimes. Hybridizations to create said gene expression profiles were done using ChondroChip (version2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who have depression, having non-depression or normal. The "*" indi-

cates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for patients with depression, non-depression and normal are shown. 941 genes were identified as being differentially expressed with a p value of <0.05 as between the patients with depression and a combination of those individuals without depression and normal is noted. The identity of the differentially expressed genes is shown in Table 3N.

EXAMPLE 24

**[0289]** ChondroChip Microarray Data Analysis of Gene Expression Profiles of Blood Samples from Individuals having Osteoarthritis as Compared with Gene Expression Profiles from Normal Individuals

**[0290]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients who were identified as having various stages of osteoarthritis as compared to blood samples taken from healthy patients.

**[0291]** Osteoarthritis (OA), as used herein also known as "degenerative joint disease", represents failure of a diarthrodial (movable, synovial-lined) joint. It is a condition, which affects joint cartilage, and or subsequently underlying bone and supporting tissues leading to pain, stiffness, movement problems and activity limitations. It most often affects the hip, knee, foot, and hand, but can affect other joints as well.

**[0292]** OA severity can be graded according to the system described by Marshall (Marshall K W. J Rheumatol, 1996:23 (4)582-85). Briefly, each of the six knee articular surfaces was assigned a cartilage grade with points based on the worst lesion seen on each particular surface. Grade 0 is normal (0 points), Grade 1 cartilage is soft or swollen hut the articular surface is intact (1 point). In Grade II lesions, the cartilage surface is not intact but the lesion does not extend down to subchondral bone (2 points). Grade III damage extends to subchondral bone but the bone is neither eroded nor eburnated (3 points). In Grade IV lesions, there is eburnation of or erosion into bone (4 points). A global OA score is calculated by summing the points from all six cartilage surfaces. If there is any associated pathology, such as meniscus tear, an extra point will be added to the global score. Based on the total score, each patient is then categorized into one of four OA groups: mild (1-6), moderate (7-12), marked (13-18), and severe (>18). As used herein, patients identified with OA may be categorized in any of the four OA groupings as described above.

**[0293]** Blood samples were taken from patients who were diagnosed with osteoarthritis as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease. In each case, the diagnosis of osteoarthritis was corroborated by a skilled Board certified physician.

**[0294]** Total mRNA from a drop of peripheral whole blood taken from each patient was isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample were generated as described above. Each probe was denatured and hybridized to a 15K Chondrogene Microarray Chip (Chondrochip) as described herein. Identification of genes differentially expressed in blood samples from patients with disease as compared to healthy patients was determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002).

**[0295]** FIG. **22** shows a diagrammatic representation of gene expression profiles of blood samples from individuals having osteoarthritis as compared with gene expression profiles from normal individuals. Expression profiles were generated using GeneSpring software analysis as described herein. Each column represents the hybridization pattern resulting from a single individual. Normal individuals have no known medical conditions and were not taking any known medication. Hybridizations to create said gene expression profiles were done using the ChondroChip (version 2). A dendogram analysis is shown above. Samples are clustered and marked as representing patients who presented with different stages of osteoarthritis or normal. The "*" indicates those patients who abnormally clustered despite actual presentation. The number of hybridizations profiles determined for either osteoarthritis patients or normal individuals are shown. 300 differentially expressed genes were identified as being differentially expressed with a p value of <0.05 as between the osteoarthritis patients and normal individuals. The identity of the differentially expressed genes is shown in Table 3O.

EXAMPLE 25

**[0296]** Microarray Data Analysis of Gene Expression Profiles of Blood samples from Individuals Undergoing Therapeutic Treatment as compared with Gene Expression Profiles from Individuals not Undergoing Treatment

**[0297]** This example demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from individuals undergoing therapeutic treatment as compared with gene expression profiles from individuals not undergoing treatment.

**[0298]** Blood samples are taken from patients who are undergoing therapeutic treatment. Gene expression profiles are then, analyzed and compared to profiles from patients not undergoing treatment.

**[0299]** Total mRNA from a drop of peripheral whole blood taken from each patient is isolated using TRIzol® reagent (GIBCO) and fluorescently labeled probes for each blood sample are generated as described above. Each probe is denatured and hybridized to a microarray for example the 15K Chondrogene Microarray Chip (Chondrochip), Affymetrix Genechip or Blood chip as described herein. Identification of genes differentially expressed in blood samples from patients undergoing therapeutic treatment as compared to patients not undergoing treatment is determined by statistical analysis using the Wilcox Mann Whitney rank sum test (Glantz S A. Primer of Biostatistics. 5th ed. New York, USA: McGraw-Hill Medical Publishing Division, 2002). Expression profiles are generated using GeneSpring software analysis as described herein. The number of differentially expressed genes are then identified as being differentially expressed with a p value of <0.05.

**[0300]** All patents, patent applications, and published references cited herein are hereby incorporated by reference in their entirety. While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

**[0301]** One skilled in the art will appreciate readily that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those

objects, ends and advantages inherent herein. The present examples, along with the methods, procedures, treatments, molecules, and specific compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention as defined by the scope of the claims.

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<222> LOCATION: (270)..(270)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<223> OTHER INFORMATION: n is a, c, g, or t
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<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (400)..(400)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<223> OTHER INFORMATION: n is a, c, g, or t
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<222> LOCATION: (426)..(426)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (433)..(433)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or t
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<222> LOCATION: (452)..(452)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (460)..(460)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (463)..(463)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<222> LOCATION: (471)..(471)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (495)..(495)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<222> LOCATION: (500)..(500)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (504)..(504)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (516)..(516)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 2

gcctgttcta tacagnttnt aaatntcatt tcagatcntn tntntgtgat aatgaatgct 60

gttnnntagn natcctatat natgtncgna cacatcctaa agcataggat gaaaaantga 120

nanccttagg atttngagca cantgccttt acctgaatat atacagcaca gttctgnant 180

ncctggcgtg tgnnactgga gatctctann aaaangnata nagtgggngg gcnctntggc 240

gcntgccggt nnnncctaaa ttttccccan gngnnggagg ccngtcacct gnncccatng 300

cgntctngac cngcctgtna acgnntanng gagccttagt cnctnctaaa aacacaaaat 360

tagccnggca tgggggntgg gnccccttgta ntctnagctn cttgggaggc tnngccagga 420

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antncncttg aanccgggna gngggtggcc tnaagtttgn ggnaaggcca ntgatcaccg 480

ccccttcccc tccangcccn gggngaaggg atttgngact tccgttttgg 530

<210> SEQ ID NO 3
<211> LENGTH: 215
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 3

cggcacgagg atcaatttgc cttggaagaa caaaaggaaa gtctggaaat gcagaaagta 60

tggatgctga accacataac agcagatggc attgctgtga agtatactgg atggaataca 120

ttcaagcgtt aatatttaat tctttttgtg gaaggtcaca caattaaaat ttaattgggc 180

atggaggctt aggacggggt aaaaaagtct ttaga 215

<210> SEQ ID NO 4
<211> LENGTH: 129
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 4

gtttctttttt cctaaaacgg ttttatttaa ctcaatgtgt caaagttttt ttttaataat 60

cccaagaggg atgaagccgt gtccacaggg atatatacat cattatggtt cccatctttc 120

atacatgaa 129

<210> SEQ ID NO 5
<211> LENGTH: 361
<212> TYPE: DNA
<213> ORGANISM: Human
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<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(21)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (25)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (65)..(65)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (77)..(77)
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (102)..(102)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (117)..(117)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (127)..(128)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (169)..(169)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (172)..(172)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (192)..(192)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (203)..(203)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (243)..(244)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (248)..(249)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (253)..(253)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (283)..(283)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (288)..(288)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (299)..(299)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (318)..(318)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (327)..(327)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (334)..(334)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (348)..(348)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (359)..(360)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 5

ggggggctttt ttnnancggn nccgnnnncc cttcctggga antttgggc cnttntntna 60

aangnggnct tncnggnaaa tgggtttttt nagggggctg gncaaaggtt ttttctntaa 120

tgggatnngg ccggcatttt aaaaaaaccc gctttggcct ttttgctana tnggaaaaaa 180

ttttttaaa angcctaaga canggttttc ccttcatatg ccaaactttc cctaacattt 240

ggnnttttnng ggngggcagg gggggatttt taaaccggat ttngggtnaa aaaaaatcng 300

gggggaattt ttgggganaa aaccttnggg gggnccccct ttgaaaanaa agggtgggnn 360

g 361

<210> SEQ ID NO 6
<211> LENGTH: 839
<212> TYPE: DNA
<213> ORGANISM: Human
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<222> LOCATION: (475)..(475)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (556)..(556)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (559)..(559)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (585)..(585)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (606)..(606)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (644)..(644)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (671)..(671)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (693)..(693)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (695)..(695)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (714)..(714)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (742)..(742)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (744)..(744)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (756)..(756)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (765)..(765)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (768)..(768)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (808)..(808)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (815)..(815)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (823)..(823)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (830)..(830)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (837)..(837)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 6

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ttgtcaatca tttattggtt ctaaaaagga tcggacaatg tgctatttca gggaagccaa 120

tgttttggag taaaatgcac aaataatttc tcttgccttg caaacacatt tttttttctg 180

tcattgcaat gtgcacaaag ggccacgagg atctacaaga aagcctgcct tattctgacc 240

aggagtgggg agctgacaag aggcttcaca gagcaggtga tgtttagaga ggaatgtctc 300

ccatttccta gtagcctgtg aggctctcaa aaccgggaat caagtttccc ttctgaactc 360

agttctcaat cgtgtaggga tagggttccc aggtgtgcct ctatgtgtag aggctctatt 420

ataccctgga tacacattga tatgcatgtg caatgctgga atcaccagcc cccangtcct 480

cctcccaaat gtgcatgttt tttgacccat gtcacattta atttttttt tcaattgacg 540

ggtttttagg gcaaanttnc caaaacatcc cccactttgc catantcccc tgtcattcca 600

tattgncttg cactgacatg attcactcat tgatattgcc tgtngcgttc ctatggcctt 660

tgagtttgca nactgggttt gggggaaacc cangnaaaaa aacctctttg aaanggggaa 720

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cccccccaat ggtgggggaa ananaactgg actttntttg ggagnccnga atttgctctt 780

gaccaggcag ggacctggga ccctgaangc ttttntaatc ttnggggccn gaaaatntg 839

<210> SEQ ID NO 7
<211> LENGTH: 118
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 7

atgggaaagt gtgtaagatt tagaaaaagc attaactatt agtaaacttt atcttaagct 60

ctaacctttg attaggtccc acaaaaatta ggtgatatgc aatttctaat ttagggcc 118

<210> SEQ ID NO 8
<211> LENGTH: 197
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 8

gttgcagtga gccgagatca taccactgca ctccagccta ggcaacagag cgagactcgg 60

tcaaaagaaa aaaaaaaagg ggagctgggc gtgggtacta atgccgtaat cccaggcctt 120

tgggaatccc aggcaaggtg gcctttaggg caaggagttc ggaacctccc tgctaacagg 180

taaacccct ttccctt 197

<210> SEQ ID NO 9
<211> LENGTH: 250
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 9

gagaccaagg ccgccccgct ctggtctcag accagttgtg ctgctcttgc tctggctcag 60

ctggtgtggg gcgcaggcgg gaaacgagac ctctagcatc tggctgaagg ctctgccaag 120

ctcctcttca gggctgcagt ctgcctgcct gcatataccg acttggccag acactgctgc 180

taaattccag ggactctttc tcccctcctc tgctctccag ccaatccttg aggatttaat 240

aactggaagg 250

<210> SEQ ID NO 10
<211> LENGTH: 680
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (433)..(433)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (600)..(600)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (615)..(615)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (626)..(626)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (645)..(645)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (661)..(661)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 10

caccaaagaa gcaagagggc tttcttttgt ttctggggac aataactaac tttaatttgc 60

tcttcaagaa gaaggaagct gggtatatag gggaatggca gaagtgctcg cagatgaacc 120

atgaggagca tggtctttaa gaacatgctg agaaggaagc aacacagact ccatcactgg 180

gggaagcacc tgaatagagc actggtaaag gccagtctgt ggacctgagg ccagaggaga 240

tgccaggggt ccagatttca tggcccacag aaacggaact gatcatattt ggttgctggc 300

cagtgttcca tagaccaaga aggctggtag caagtataga ttcctctaca tagcttgaca 360

ggagaagaga aaggggaatg tagcacacag gatgcagcag gtgaataaga aaacctcctt 420

ttcccaggtt ggngacagtg agtgatctac agtgatactc aaaagattgt gattggtgtg 480

ggaattcctg tctcaatatg caatctgcca agaaaacact gtgatggttt cctgtaaagt 540

aaccctcttt tcttatctct aatttcacaa gactcttaaa tgagaggggg gggagaaagn 600

gttctttctc actcncctaa aactgngggt ctgcctggag aaaanctaca tctgcacaga 660

naatgctggt tagccaggaa 680

<210> SEQ ID NO 11
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 11

cctgcagagt actccatgga aacaattgcc gagcacgtgc tcgcaatttg ccgagcacgg 60

tccggtttga actcctagac taagactagg taggtgatac ataccttctt cccaccaagt 120

actcacgatc caaactatga attttagatt cggatcaaac gaggattgat ccgagggacc 180

aacgttgtga taaatcttac gtcgtcttat atattaagtt tttgtggagg atcggataag 240

tctatagtgt ttgtcacaga tagtcccgta ccacacccca gaccatagga gtcgctctcc 300

ggaccgcggt ctaatggg 318

<210> SEQ ID NO 12
<211> LENGTH: 155
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 12

tctcacattg gacatactca aaattcactt ataatcttca caccaccaaa aacttaccca 60

tatcaaatta taaacccacc cacattactt aaaatttttt acatttccca ataaaaaacc 120

caaataaaca aaaacttcca atctccattt aaaat 155

<210> SEQ ID NO 13
<211> LENGTH: 125
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 13

aataaacaaa catgccctct aatatatgaa ttcatcacac aacacgcaca ctgtccccac 60

aaacaccttt ttggtgtcaa gaagaaaaag actagcttca ctgaacagag aaatgctgga 120

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cagtg 125

<210> SEQ ID NO 14
<211> LENGTH: 168
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (56)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (94)..(94)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (127)..(127)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (155)..(155)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (157)..(157)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 14

ggcccntggg ggggnagggc cttttcgggg ccggggnngg gccccnnttt ggcccnnggg 60

gggtttcccg gggaacccaa ccctttaagg ggtnggggggg aatttccccc caaaaaaagg 120

gaaaaanttt tccgggggggc ccacccggga agggntnccg gggaaggg 168

<210> SEQ ID NO 15
<211> LENGTH: 438
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 15

aaaaaacttc tttatagtcc ttatatattt ttaattgttt atgttagggg aagctataga 60

ggaacaaatt tgggatagaa atataaggct gggattacag gcatgagcca ccaagcccgg 120

cccacatttc catttttaat atatactgtg ctttacaaat attataatat gttttaaaat 180

atgttcacag aagcacctgg tctgtgaatg gcatgccagc attaaaaaaa ataagcattc 240

tttgaatata tatttagttt tttaatgtgg taggaaaatc aaagccagag ggagtagaaa 300

caaaatttgt gattttctaa atacttcttg gctgcaggga agaaaccacg tcccaggcga 360

agtcctacct aatttgatga taaaattaca tggaagggat tcttgttggc atgaggacct 420

accaagatgg tcaacaga 438

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<210> SEQ ID NO 16
<211> LENGTH: 235
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (154)..(154)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (207)..(207)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (217)..(217)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 16

aaggnctttt ccggnccggc ccggcccccc ttggcccang ggggttnccg gnaaaccacc 60

ctttaaggnt tgggggaatt cccccaaaaa aggaaaaaat tttcccgggg gcccacccgg 120

aaaggggggaa ggcccccaaa accgggggggg gggnaaaaag gtgggtttcc ccctttttcc 180

aattcccaaa accaatttcc aaaaggnaaa ccaaccnttc ccaaaatggg aaagg 235

<210> SEQ ID NO 17
<211> LENGTH: 294
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(19)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (66)..(66)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (133)..(133)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (162)..(162)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (210)..(210)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (260)..(260)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (276)..(276)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 17

aaaccaaccc tttaaggnnt ggggggnaat tccccccaaa aaaaggnaaa aatttttcc 60

gggggnccaa accggnaaag gntttgggaa aaccaaattt tttttggncc caacccccc 120

caaattgggg ggnaaaccaa atttaagggg ggaaggggg gncccccccg ggaaaggccc 180

aaggggggaa aatttttccg ggggtgggtn gggggaacca atttaagggg ggggccccg 240

gggggttcc ccttgggccn tttttccttt tgggtnaaaa aaaaaaaccc cttg 294

<210> SEQ ID NO 18
<211> LENGTH: 453
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 18

gtagaatata gggtgatact ggagatctac tgcgacctag accatgatac ataaccacac 60

aagtttaatc cctgggttct aactaccctt actgtcactt agcttaacct gcctccaatc 120

ctgtacttga actctaaaac tgttggagaa actcagtgct taccccaaca gattcatttc 180

aaatagctgt aaaaggtatg tttactccag aagaccagag ttgcttcttt tgaacttctc 240

attccttggg cctaggaacc ctcatcaccc tcatcccaac gtcaacccag atcttctctt 300

ccataaacag cactccctca ggcccctgcc tgacacaggc atagactgtc atgttggatt 360

cacagacagg ctgtgctaga ggaaacctct ggggctcacc aggggccgtg ggatgggctt 420

ctggggcttc ttggagccca acttcttcat ggc 453

<210> SEQ ID NO 19
<211> LENGTH: 242
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (165)..(165)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (189)..(189)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (216)..(216)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (221)..(221)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (230)..(230)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 19

gagtcagact gtaaggnacg aaccctcggg gtccccacgn tgttcccccc ggggtaacnt 60

cggcccgggc ccgggnagcc cttcccgggc ttttcccccg gggggggnccc gggggggacc 120

tttaggcggc accccaacaa caccaggccc tacttttttcc aaggncgggg aagcccatgg 180

gttctgggna acgggcaatg cgggcttgca acgggnggaa naaaaacagn cccaaaagaa 240

tg 242

<210> SEQ ID NO 20
<211> LENGTH: 181
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 20

gtttgtttgt ttttgagatg aatctcactc tgtcgcccag gctggaatgc agtggtgtga 60

tctcagctca ctgcaacctc cacctctcag gagaattgct gaacctggga ggcggaggtt 120

gcagggagct gagattgcgc cactgccctc catcctgggc gacagagcaa gaacctgtct 180

c 181

<210> SEQ ID NO 21
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (23)..(23)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (62)..(62)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (70)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (83)..(84)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (86)..(86)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (97)..(97)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 21

gcacaaggaa gggtggncag atnttccngc actggnaaaa ngcngctatg gtngtgaant 60

tnccccnccn nttnanacna aanntngcac tcttggntgc 100

<210> SEQ ID NO 22
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (52)..(53)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (56)..(56)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (77)..(77)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (85)..(85)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (96)..(96)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 22

cntgcgccat ttactgnagg tggacaagga tactatnaac aaagatgtgg cnnaangaga 60

ataatggaag atagctntga ggatnaacnc tggttnaggg 100

<210> SEQ ID NO 23
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(29)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (46)..(46)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (65)..(65)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (72)..(72)

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 23

acaccttccc acttgcngna aaggggnnng gcccccnnct tgggcnganc attaagcctt 60

tttgnggctg cngcccctgt gcctggtgcc acaacaaatg 100

<210> SEQ ID NO 24
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (109)..(109)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (157)..(157)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (177)..(177)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (199)..(199)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (207)..(207)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (211)..(211)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 24

ccggncacca ccnttaaggt tgggggattt ccccaaaaaa ggaaaatttt cggcggccaa 60

cgggaaggcc nttggggaaa aaaccaangg ncaaaccccc ccaaccacnc ggcccccccc 120

aaggggggtg gggaagagcc aaatttcttt gggaaanaac gccccttgg ggaaaanaag 180

gccaaccacc tttcaacanc ccccaangcg nggaagccat ttcttgg 227

<210> SEQ ID NO 25
<211> LENGTH: 306
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 25

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tccaaaagta gagcagaggg atattttgtt ctactgagcc acgaaaaaca cctgaattgt 60

ttcgaccatg tgccttccca ggttgatgaa gacattgcta cacagtctgc agatcaggaa 120

ggaagaattg tatgtgggag tttttaatgg tctcatttca ttggctataa ctcagttaca 180

aggagaaata taactgcaga ggagctttga aaatttagtt cagctgaggg taaaggaaga 240

agagacaaat tttgtcatca gctagtgatc tgccatacaa ggtgttccct taatatgtgt 300

agaatg 306

<210> SEQ ID NO 26
<211> LENGTH: 492
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (299)..(299)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (333)..(333)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (353)..(353)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (410)..(411)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (460)..(460)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (474)..(474)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (479)..(479)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 26

cggcttcggg ccaagcgttt ccagagtttg ccgaactgct gagcaagttc gctattctcc 60

agatcgccta gccctttgcg ggcgaccacc acgatgtccc agcctgtcag gttgtcctga 120

ttgaggcgaa aggactcgcg gatttgacgc ttgatgcggt tgcgctcgac ggcgagcttg 180

acgctctttt tgccgatcac caaacctagg cggggatgat caagctggtt atcgcgcgct 240

agcagcagga cacttttgcc cgggagcttt accgcttggg gagtcgaaga ctgccttgna 300

ttgccgggga gtcagcagtc gctttttccc ggncgaagcc tcgaactcac cancctgtct 360

ggattaatta gacagcaaga cgcttgcggc ccctttggcg cgaacgaacn ncgaaaagga 420

cttgcgcggc ccgtttcttt ggggggccaa taccggggcn cggggaaaac ccgnggggng 480

gccaaacccc cc 492

<210> SEQ ID NO 27
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (348)..(348)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (422)..(422)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (435)..(435)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (476)..(476)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (490)..(490)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 27

cgaagcgatg gaagcgcaag cttggtaggg gagcattccc acggcagaga aggtcgggcg 60

acgagccggg ctggagcggt gggaaaagca aatgtaggca taagtaacga caatgcgggc 120

gagaaccccg cacaccgaaa ggctaaggat tcctccgcta tgtcaatcaa cggagggtta 180

gtcgggtact aaggcgttag cgaaggcgaa gcgccgatgt gaaggggggtt aatattcctc 240

cacttgccat gcgtgtgaat ccatgacgga gacgaagccg ggggtgcgtc ctgacggaag 300

tgggcgccag caggggcggc cttcgggcca aaccgaacct caggtcanac ttccaagaaa 360

agtgggtgaa acgccagcgc atggcaaccc gtaccgcaaa ccgacacagg tagccggggg 420

anaacatcct aaggngctcg agagtacttt ctagagcggc cgcgggcccc atcgantttt 480

ccacccgggn ggggtaccag 500

<210> SEQ ID NO 28
<211> LENGTH: 231
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (138)..(138)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (174)..(174)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (176)..(176)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (211)..(211)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 28

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aagaaattcc gggcacgnag gcacgcccct ggtaattccc caggcgnact tctggggang 60

gctggaaggc ttgnagggca gaaaagggat ccgcctttgg gaggaaccca ggtaaggttt 120

aagaaggaac ccaccctngg ggccaaacaa aaacttaaaa acccccccat ttcntncccc 180

ccaaaaaaaa aatttttaaa aaaaattttt ngcccccggg ggcattgggg g 231

<210> SEQ ID NO 29
<211> LENGTH: 109
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 29

nncgaacaat angtctggag ctcgtgcgnc ctgnaggtgc gacactagtg gatccaaaga 60

attcggcacg agggattaca gtcgtgagcc actgcacctg gctgcaatt 109

<210> SEQ ID NO 30
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(6)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (32)..(33)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(50)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (78)..(78)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (87)..(87)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 30

tcnnnntntg gtntnggctn tccgagnggc anngagtgan tgcccgttnn tattgancac 60

cantcantng ttgccntntg atacccnana caaaattgaa 100

<210> SEQ ID NO 31
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (46)..(46)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (60)..(60)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (69)..(70)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (73)..(73)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (96)..(96)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 31

tcgggcgggg ancccttac ctgtcnttac gatgcgcaag tagatnccng atttngtccn 60

ganggtcgnn aanttaggnt tccagcctgc gncacngcca 100

<210> SEQ ID NO 32
<211> LENGTH: 104
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(64)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (73)..(73)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (75)..(78)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (90)..(90)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (96)..(98)

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 32

cntgctntta cgatgcgcaa ggtagtnccg tgantttagt ccgtgatgtg tcgaaanatt 60

agnnttncag ccngnnnnan tgccattttn gctctnnnga gaaa 104

<210> SEQ ID NO 33
<211> LENGTH: 102
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 33

tgggntggcc cngcttaact tttgcccncg anctcggngt tcgnacaggg gcgaagnaaa 60

ccgccaantt ttttcnaacc cnacttgttt tnggttttag tt 102

<210> SEQ ID NO 34
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (21)..(21)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (50)..(50)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (73)..(73)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (78)..(78)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (85)..(85)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (97)..(97)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 34

agnacgcctt tacagcttta ngatgcnnga gagagtancg gatttgnccn tgntggtgga 60

naaattaggg ttncagcntg tgnantgcca ttttcgntaa 100

<210> SEQ ID NO 35
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (21)..(22)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (65)..(65)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(68)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (77)..(77)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 35

cacgatagca tcagacggcg nncttggngc cnttttgccc gctggtcaca ggacaacgca 60

tttcncnntn tggtgtncgg ctntcacgca tnggcgcgag 100

<210> SEQ ID NO 36
<211> LENGTH: 153
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (43)..(44)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (46)..(46)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (98)..(98)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (115)..(115)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (117)..(118)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 36

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tggngccntt ttgcccgctg gtcacaggna aacgcatttc acnntntggt gttcggntnt 60

cacgcacggc agcgagtgca atgnccgatt cattcttnaa cgacgcacac acccngnngc 120

cctgtgaaac ccataaacag tgggaaatgg tgc 153

<210> SEQ ID NO 37
<211> LENGTH: 151
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (65)..(66)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(75)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (94)..(94)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (126)..(126)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (141)..(141)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 37

gcgcgcntgn aggccccgac actagtggat ccaaagtatt ttggcacgag ctnagttcga 60

ngatnnagac cncnnatcac ctaatacanc catnactcan atgactnttt gtgcgccttt 120

tatcanatgc atagcctatc naaaacatca c 151

<210> SEQ ID NO 38
<211> LENGTH: 100
<212> TYPE: DNA

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<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 38

gngcgcttgn aggccgacac taggggatcc aaagaattcg gcacgagctc gtgccgaatt 60

ngncacgagt tnggctgcnt ctttatacaa cttttcttca 100

<210> SEQ ID NO 39
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(16)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 39

aaagngnntn ctggnnttan gcanttaacc caggcactgg ggcgctgaac agctactcag 60

ctgcttaagt ngtcccactg gtccagacca gcgacccagc 100

<210> SEQ ID NO 40
<211> LENGTH: 102
<212> TYPE: DNA

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<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 40

ttcccccagg atctttctta tatctatcag atctaggtga aaggattact gtcttgtagg 60

tgtcctgaag gacaagccgn ttcgtttgaa nctgtgaaat ac 102

<210> SEQ ID NO 41
<211> LENGTH: 325
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 41

ttcggcacga ggagaagaga ggagccgtca gaacatatgg gggatgtgtt caagaagcag 60

atttgtggtc ggaagctttg caaagagggg acctgggtct gagtgacatg cgtggccact 120

ggtgctcctg cgtttggact gtgcaggcct ctcctatgct gatgcgtctc cccactcctg 180

agctaatttc tgctctgctc cttctgtgac atgtggcagc gtgggaaata gccactgtcc 240

cctgtccctg ctgttcctgg tgtcacccag caccaggcca ctctgggagc cagggcagat 300

ggtcctccct gtggtcctgg cctct 325

<210> SEQ ID NO 42
<211> LENGTH: 103
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (73)..(73)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (98)..(98)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 42

gtggcccaag gggnactgaa ggggccctcc ntaagnggag gggttgggga gtaaggcctg 60

ggnaggaccc tgntgactcg gggggcggga gcngggancc agg 103

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<210> SEQ ID NO 43
<211> LENGTH: 221
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 43

catattttga aatacttttc tcccaaactg ggtttattag cgtgtaccct gcttttccac 60

tttaaaaatt tatgccatat gtccagcttc cagtcagtgc ttctggttag catgaggata 120

actagatttt actgtagatg gtagataaaa gtccagtgaa aagcaaagat gtgtaatgtt 180

ttggtagcct cagtgctctt atcccaagta aaagcaaagt t 221

<210> SEQ ID NO 44
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (27)..(28)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(39)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(50)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(62)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(68)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (79)..(80)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (85)..(85)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (93)..(93)

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 44

anagagatca ntgatttatt gctgggnncc tgtntganng ntctaaggnn tgaagattat 60

nncattnngc aagcgnacnn gcgcngccna gcngaccagg 100

<210> SEQ ID NO 45
<211> LENGTH: 106
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (33)..(34)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(48)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (58)..(58)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (73)..(73)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (77)..(77)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (95)..(96)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 45

atatttcngg agcttgcagc ggcnacacta ggnnactaaa agaattnnag aaagaggnct 60

atnggacnag nanacangaa acctgcanac ttggnngctt ggaagt 106

<210> SEQ ID NO 46
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 46

gatgtggaga tgcttgatag gttactgggc ggcaatccag gagttgatga agcgcatatg 60

cgaacatttc acgngcatat tgcggtgcaa gggcttactg 100

<210> SEQ ID NO 47
<211> LENGTH: 101
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (23)..(23)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(48)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (60)..(60)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (62)..(62)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (66)..(66)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (70)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (86)..(87)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (96)..(96)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (99)..(100)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 47

ccccccnncc cttcttntcc ccnaaagaat aanataagaa tngctannga gnaancgacn 60

anggtnttan nagntatatg tatntnncaa accaantann a 101

<210> SEQ ID NO 48
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (35)..(36)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (46)..(46)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (81)..(81)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (87)..(87)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (94)..(94)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (97)..(97)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 48

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aaggnnaggc tcgttggggg aaaaaacccg ccntnncggg cncccngnaa acccncacna 60

ggggacccna aaaaccggaa naaaccnccc nagnaancca 100

<210> SEQ ID NO 49
<211> LENGTH: 473
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (164)..(164)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (178)..(178)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (201)..(201)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (211)..(211)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (274)..(274)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (305)..(305)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (340)..(340)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (346)..(346)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (386)..(387)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (405)..(405)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (433)..(433)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (446)..(446)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 49

atgagtatga aatgaaaggn tgagatgaaa tgatgatntg agatgagatg aaatgagatg 60

aaaccgagat gaaatgatga aatgatgaga tgagaccgag acgaaatgat gagatgaaat 120

gagatgagat aaaatgagat gaaatgaagt gaaatgaaat gaantcctga aattgacntg 180

agatgaactg agataaaatg ntgagatgaa ntgatgagaa gaaatgagat gaaatgagat 240

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gagatgatga gatgaaaaat gctgagatga aacntgatga gatgaaatga tgagatgaat 300

tgaantgaaa tgaaataatg aaataatgac ctgagatgan atgaantgat gaactgatga 360

actaatgaaa tgaaaatgaa atgganntga tgagatgaga agaantgctg agatgagata 420

aaatgagatg aantgatgag atgaantgaa atgctgagat gagatgagat gaa 473

<210> SEQ ID NO 50
<211> LENGTH: 453
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (22)..(22)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (65)..(65)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (90)..(90)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (94)..(94)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (96)..(96)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (98)..(98)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (102)..(102)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (104)..(104)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (113)..(113)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (115)..(115)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (117)..(117)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (121)..(121)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (123)..(123)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (125)..(125)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (128)..(128)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (142)..(142)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (144)..(144)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (160)..(160)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (174)..(175)
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gatanggccn gnaagcaatn tanaggatan ccgnangnta tngnaacaca ttncncnagc 120

ntntncanca gctgatgcag gncncctatg atgcgattan ggactacgac tatnnctcan 180

ngtctnaaca gncgcgangg ctgantacta aaagnacaca aanntgtgca ccnncatnac 240

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tcncgttgac tgnacantgt agacctgnaa tacctggctn aaaggggtct nactgncatn 300

agagntgnag ntgcccctnc antagngnga gctnnaannng gcctgtnttt gntttacntc 360

ntcgganagg cgatgccatt anagacccna gaacncattg gtgatatacn ctnnaccngg 420

agggnttaca ttgggnaatg atnattatgg ggg 453

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 51

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cttgtttaga cttgcatctg cacatagaag tagggatttc atgctgttat cagcctaatt 180

ttagcctata gaatttcaag ttngctagag gtttngctct ccatggtata agtttagcaa 240

gaaaagtcat ttgtctgctg ctctagcagg ttanaatgtg gaagtatagt gtgcanagtt 300

ttaatccgna tatgttatta aaacatatac atcattttat atcatacatc tgnaataaat 360

attcaaaatt aaatagtgat ttgggattga ttacatctta ttactagctg taataaatga 420

cctcnnngat ngtttaaaat tgttttcctc ncatataata aaaatacctn angcatanat 480

cgattgtcca aaaattgaat atatatacac acctcttcca ttagaactaa atatgtggaa 540

tg 542

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<221> NAME/KEY: misc_feature
<222> LOCATION: (679)..(679)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (689)..(689)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (695)..(695)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (698)..(698)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (711)..(711)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (720)..(720)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 52

atatgacctg cgnncanacn cnctaanang ngactngtta aanacnttcc gtggaatnna 60

ctcagactgc aaantgtnat nctgncnnan nntgnngact gtccngncng atttnnngcn 120

tgnaatacta ttgcctctta tatacacnac caannntgcg aagggcnann nnacctttnc 180

cantnnnctg gggncccacn nnngngaact gagagtggat cttgtgtacc tgacnnacca 240

gntntnnagn agggcgctca ctctgattgg tgcaccatgg ttacacagtg tgtgcaaaga 300

ccngnctatc tcactganga tgattgncag ngccnntggg tggcacnang ggnactgatg 360

ancancactg accctgccga cgccagangc cgcanatccg gagantncat gngacnatat 420

aggttaccnc cttcnaccgg gcancaatct gcttctatgg tgaatgcaga ccatntagaa 480

ntctntcnct ataggcatga ttttnnncag tgcgtcagcc ttganaanga ancnnacttt 540

tgntagatga nnngntgctc ncccttgngg ctnacaaatt ccancaccnt tggtggcngc 600

agccnttaag ancacttntt ttgggttgcg ctnttggatg aattacnaat agnntgtttt 660

gttncaaggc ccttctgcna aatatgaana aaagngcnct tagctttttg ngggaactgn 720

actggaaatt ttg 733

<210> SEQ ID NO 53
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (44)..(45)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (50)..(50)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(59)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 53

gatcagacaa gancntggtc cacagcggga cgagagntct cnannctgcn ggggagnnnc 60

caagtacgcn agcnctgaan ctaaagcaag caagaaaaag 100

<210> SEQ ID NO 54
<211> LENGTH: 515
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 54

atatggcaag gataacccct atacttctgc ataatgaatt aactaaaata acttgcaagg 60

agagccaagc taaacccccg ataccgacga gtaccagaac aggtaagcac cccgtctatg 120

tagatatggg aagattatag gaggcgacaa ctaccgagcc tggtgatagc tggtgtccaa 180

gaagagtctt agttcattta tttggcccag aaccctctaa tccccttgta atttatgtca 240

agaggaacag ctctttggac actggaaaac cgtgagagag taagatttac acccttaggg 300

gcctaatagc agccaccatt aagaaagcgt tcgctccaca cccactacct aaaaatcgaa 360

tataactgac tcctcacacc caattggcca atcattcccc tataaaagaa ctatgttagt 420

ataagtaacc tgaaaacatt ctcctctgca taagccctgc gttggattat atcctgcact 480

gacaattaac tgccccaata tctacaatcc aaccc 515

<210> SEQ ID NO 55
<211> LENGTH: 176
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (60)..(60)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (62)..(62)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (155)..(155)

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 55

tgttnaggat caaattataa tattgaaata anaacagctn acatttatat agcatgtttn 60

cntatctcaa ctaatnataa atgggaaaat gggcaactgg gcaggcngaa cccagaggga 120

agcctgccct cattagacca agacagcaag gtttnccctg gtcactagat gaaatt 176

<210> SEQ ID NO 56
<211> LENGTH: 317
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 56

cagnagtgat gttgcaatat ctggaactag caaaggatac tgatgagaaa acgtggaatc 60

atgtgggatg tgacctccta ggactcacct tgcacagctg ggtgcagcag ggataggtaa 120

ggatttgggg tttagaggta caattgcctt tttatggtta gagaaaggtc ctggggctgg 180

agggagcctg acgatctgct ctgtgtgcaa ggggagagtt aactctgcac gcaagagcct 240

gcttaaaggg ctgtgtcagt tctattgtaa acaccaactt aaagtggtgg atgctggcag 300

acattgttat tgccatt 317

<210> SEQ ID NO 57
<211> LENGTH: 209
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 57

ctcatacacc tgtggctact gttttctaca gagtgccaaa actattcgag agaataggct 60

ctggactgga cactgtatac ccacatgcaa gatgaagttg gccccttaca tcctatacgc 120

aggagaattg cgtcatttaa agcctgttga cgcttttctc ccgcagacga atggaaagat 180

taattgggag tgggggctga aacaattcg 209

<210> SEQ ID NO 58
<211> LENGTH: 262
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 58

aattttgctg ttacatggtg gctcaactga gtcccatact ttgaaggccg ggagttaatc 60

acctggtcac cgagttgcga accagcctcc aatatgtgga accctgtact ctctaaaaat 120

caaatcaccg gcatggagat tgcgcctgtg gtcccaaaat actcgggctg ggacacgatg 180

agttgcttgg cccaaggaag gagggttgta tggctgatca cactggtccg cctgggtgac 240

agagcgagac tccatctcta at 262

<210> SEQ ID NO 59
<211> LENGTH: 430
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 59

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gtcagtttat ttctgactag ggatattttc tttccattta gaaaagaaga aaaaaaaaaa 60

aaacctttat tgtcttacag gggggaacta gcgcggggct gaataaaacc tttggccctt 120

cccgggggag gggtatccgg tttataaacc ccaagggtat tttcttagca aaatacttaa 180

aaccggccgg ggtttttata caaactggga acccactttt gaaaaatttt ggccttttga 240

tctgggatgg gaatatgagt ttttatacat ttcattttct ttttgggcaa aggcccggtt 300

aagtattccc ccccgggggg cctttacaaa aagggcggtt ttaaaagctt ttgggccccc 360

ctagggaatt gttttaacac ctaaaaaccc ctgcttccct taaaggggcg ttctttaatt 420

tgggggcggc 430

<210> SEQ ID NO 60
<211> LENGTH: 350
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 60

aaacctctct aactatatat cacaataacc tgcgcataag atttacgctc cgatcttttc 60

atcctactag cttggaggat ttgaaccgat tatgaatacg caatactccc ggtcctcatg 120

tatcatgtgt aagcccatct cctgggaggg ctaacatact accatctcca aggagaggca 180

tgattccgaa tcacccacag acagctcgat caccatacgt atcacccaac atatatacct 240

tctaagactt gctagaaaca accaccacat ttgatgctta atcaccactc tgacgcgcat 300

taaagtgagg ggactctcct aatttctgta agttgatttt tgcattctga 350

<210> SEQ ID NO 61
<211> LENGTH: 515
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 61

cacataaatt ctccataagt taattagtga ttttaacatg atctcaatat aaacatagca 60

cactttcttt gagaattcaa catattgcaa gttaaaattt tcatagacta cacaagaaag 120

aataatcagg caaatcctta agaataaggg caattaagga tgactagccc tacaagattt 180

taaaaaggat tcattagttt aaaaaatgtg atgtagatac atgaataaaa taaaatcttg 240

aagtagatcc aaatatacat ggtcagattg aatacaataa agatggcatc gtagcagtgg 300

agaaaagaag aattatttca taaaccttgt tggaatggct aggcaatcat ctggaaaaaa 360

atgaagttga ataataaaaa tatattctac actagcacaa attataaata aagcagtgat 420

ttaaatgaga aaaattaaat cataatgatt tcaaagataa cataggataa tttctttata 480

gtcttctaaa atatatgact ttatgaattc tgact 515

<210> SEQ ID NO 62
<211> LENGTH: 611
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 62

caagtacttt accaactaag ccaatcttgt ccccagccag gcatttctat acaaagggcc 60

aagactttgg ttttataaat aaggaggtat atataaatta tatatatttc tgagctgagt 120

aataatccac cagatacaag tttgcatcaa cttctgtgaa atatttttt tccttttgt 180

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tgggcatttt tatggtctaa atatagaatg accaatgcct ctagaacaaa cttgacctgg 240

tcagtgttat caagaagcag actgtttctt actttctttg tatttcctta cttatttaaa 300

tttgttaaaa ttgatatatt gatatataaa acttcttttg ccagtgttgg tggcacacgc 360

ctttaatccc agcacttagg aggcagaggc agggtggatt tctgaatttg agggcaggct 420

agtctacaga gcaagttcca ggtcagccaa ggctatatat agaaactctg gcatgaaaaa 480

ccaaccaaac caaaccaaac caaaccagac cagaccagac cagaccagac caaaccaaac 540

caaaccagac taaaccaaac caaaccagac cagaccagac cagaccagac cagaccagac 600

cagaccaaac t 611

<210> SEQ ID NO 63
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 63

ccgagagatt ggccactgct taaactcatg cagctcctac tgttcttcaa ttaatgcctt 60

taatgcgaat atacttcctc ttctttttgc atggtcttgc ccagcctctg caatactgat 120

gaacacatgc tgaagatcat ctaactcaat atggcgcata tttctatgtc ttgctgccca 180

ggacatagga caacttcgtc gctcactagt tctaacatat taatgctggc gtaggtggag 240

aactactgca catatactct tactcggagg ctgaggcacg aggatcactt g 291

<210> SEQ ID NO 64
<211> LENGTH: 309
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 64

gccagatgcc gtgtttcctc gatgaactct ttacatcatt ggctattcag tggagtgttt 60

cattatcacc tctcactctc gcgtgttacc taactctccc tcgcagggga aatcactcca 120

tatatttcaa atgtcttgct aacagtggtt actttgctct atccttagct atacgtctcg 180

aggcacattg ttcctctatg ccccgctacg ctttgcccta gagctcggcg gtatctatat 240

cttaactgcc ctcttgatcc ttacgtgccg gagaaggtgg aggcagaaat tttgtcaaat 300

ctgattaga 309

<210> SEQ ID NO 65
<211> LENGTH: 278
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 65

tagaatggaa tggagtcgaa tgtgatggaa tggacgcgaa tggaatggaa tggactcgaa 60

tggaataaag tggaatagac tcgaatggaa tggaatgcaa tggaatggac tcgaatggaa 120

agggatggaa tggactcgaa gggaatggaa tggaatggat tcgaatggaa aggaatggaa 180

tggactcaaa aggaatggaa tggaatggac tcaaatggaa tggactcgaa ttgaatgaaa 240

tgtaatggaa tagactcgaa tggaatggaa cgaaattt 278

<210> SEQ ID NO 66
<211> LENGTH: 142
<212> TYPE: DNA

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<213> ORGANISM: Human

<400> SEQUENCE: 66

agttctcctt aggttaatta atggaatgca atcccaatga aaatgtcacc aaagttgttt 60

ttttttaac tgtaggaggt ttataataat gctcatatgg aaaaataaaa catgtaaaaa 120

atagctagta aactcccccct gt 142

<210> SEQ ID NO 67
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 67

atatctgcca tcctcatcgg ccaatcgtgt tattttgatg acgaatgctt cggagattgg 60

aaagatgatc tcctcatgct tccatgcact gcgagtagaa gacatactga gcatagtgtg 120

attattttcc caacaaattg gcattcatag atagaataag ctgactaaga ctacttagcc 180

ccacattttt ttctacttgc tccaatagca ctaacaaata ggaagctctt gcttgctccc 240

caaagctcca tttccttgaa agcagaagtg taatattact tcttag 286

<210> SEQ ID NO 68
<211> LENGTH: 179
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 68

atctactttt tattcttttg ataaatgttt atgaaatata aaatactgaa aattagaaag 60

tagaagtcat tattttatta taaaacatgt ggattagata ttttcattta tgtgattaaa 120

ctttctaaac aaagattata tgaattatct taaagattta aaaagtaatt aagttaaat 179

<210> SEQ ID NO 69
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (356)..(356)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 69

cagataagac tattaagaca gataagagcc aaatcatgta gagcctcaga ggtttttgat 60

cttcagtcta agaacgtaaa tccatggaag aattttaagc aggggtgtgc cttgaccaca 120

ttttgaattc taaactgtct ctgggtgggt gtgggtgcca ccaagagcat gtgttcatgt 180

agggagactg gttttttaca gttgtctatg agagagatga cagttgcctg gattatggtg 240

gtgacattgg agataagcag gtagacagat tctcagtgta ttaggagaga aaaatcaata 300

ggaaatttaa aataaataat taactgtggc cataggagga aggagtcttt gggttnggtt 360

ctcaatttct gcatgagaaa aaaggtggac 390

<210> SEQ ID NO 70
<211> LENGTH: 481
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (26)..(26)

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<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 70

atgatgaaat gatgagatga aatgcntgag atgagatgtg atgaaatgat gatatgaaat 60

gatgacataa aatgagatga aatgagatgt aatgatggaa tgagatgaga tgaaatgaga 120

tgaaatgata gatgagataa aatgatgata tgaaatgatg agatgaatga tgagatgatg 180

agatgaatga tgaaatgaaa tgatgagatg agatgatgaa atgaaatggt gagatgaaat 240

gatgagatga aatgaaatag tgaaatgaaa ttgaaataaa atcgaaatga gagatgaaat 300

gatgagatga tgaaattgat gaaatgatga gatgtgatga gatgaaatga tgagatgaga 360

tgagatgaca tgaaataatg aaatgaaatt gaaatgagat aagatacgag ctgagatgca 420

atgagatgaa atgatgagat gaaatgaaat agtgaaatga aattgaaata aaatcgaaat 480

g 481

<210> SEQ ID NO 71
<211> LENGTH: 125
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (77)..(77)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (90)..(90)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (110)..(110)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 71

cggtngcaat tgggggccnc atacgcgcng acgagtantg gncangctnc ttgactacac 60

ngacgcgccg tacaggntna attatggnan cttacatggn aaaggggcan ctcaatgtcc 120

cacag 125

<210> SEQ ID NO 72
<211> LENGTH: 473
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (151)..(151)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 72

gaaatgaaat aatgaaatga gatgaaataa cgaaataaaa ttgaaatgag atgagaggaa 60

atgagatgaa atgttgaaaa gaaaggagga aatgatgagg tgagatgaaa tgatgagatg 120

aaatgaatct gagatgaaat gagatgaaaa ntgatacgaa aaatgatata aaaaatatga 180

cctgagatga aatgagatga aaaatgatac gaaaaatgat ataaaaaata tgacatgaaa 240

tgaaatgaga tgatatgaaa tgacataatg aaatgatgaa ttgatgatat tgaaatgaaa 300

ttgaaagatg agatgaaatg atgagatgaa atgaaatgtt gaaatgatga agagatgtga 360

catgaaatga gctgaaatga gatgaaatga aatgagatta aatgatgaga tgaaaaatga 420

tgagatgaaa aatgagatga gatgatgaga tgagatgaga tgaattgaga tga 473

<210> SEQ ID NO 73
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (233)..(233)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 73

aatgagnatg aaaagnatga aatgatgaga tgaaatgaaa tgatgagatg aaatgaggtg 60

aaatgaaatt agatgaaatg taatgagatg aaatgaaatg acctaatgaa atgaaataat 120

gaaatgagat gaaataaaat aatgaaatga tgaaataatg aaatgaaaat gagatggaaa 180

tgatgagatg agaagaaatg atgagatgaa atgatgaaat gatgagatga ganaaaatga 240

gatgaaatga tgagatgaga tgaaatatga tgagttgaaa tgacataatg aatgaaatga 300

tgaaatggaa taatgaaatg gaaatgatga gctgagatgc aatgagttga aatgagatga 360

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aatgatgaaa tgatgagatg aaatgatgaa atgaaataat gaaatgagat gaaataaaat 420

aatgaaatga tgaaataatg aaatgaaaat gaaatggaaa tgatgagatg agaagaaatg 480

atgagatgaa atgatgaaat 500

<210> SEQ ID NO 74
<211> LENGTH: 299
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (31)..(32)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 74

ggaaatcctg aagtggaaat gatgagctga nntgcaatga gttgaaatga gatgaancga 60

tgaaatgatg agatgaaatg atgagatgag atgtgatgaa atgatgatat gaaatgatga 120

cataaaatga gatgaaatga gatgtaatga tggaatgaga tgagatgaaa tgagatgaaa 180

tgatagatga gataaaatga tgatatgaaa tgatgagatg aatgatgaga tgatgagatg 240

aatgatgaaa tgaaatgatg agatgagatg atgaaatgaa atggtgagat gaaatgatg 299

<210> SEQ ID NO 75
<211> LENGTH: 155
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 75

agtgaaatga aattgaaata aaatcgaaat gagatgagat gaaatgatga gatgatgaaa 60

taaaatgatg aaatgatgag gtgatgagat gaaatgatga gatgaaatga tgagatgaga 120

tgagatgaca tgaaataatg aaacgaaatt gaaat 155

<210> SEQ ID NO 76
<211> LENGTH: 367
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (56)..(56)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (75)..(75)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 76

atagcaaaag ngggtaaaac ccctgagttt gcganannag tantcttgta ggggcnaact 60

ctacttnaga ngaantcctc gcaaaatcct tgaatcaccg cttcagtgca gtgatatcac 120

cgccatgaaa tttctgctcg attagcttac gttgtttgga tagaggccaa acaaggctgt 180

tatcggtacg aggaatggat gttcgatttc gtagaatacg cctgagagac ggcgaatact 240

ctcacgagag gcagcaggcg cgtaaattac ccaattacaa caagtagagg tagcgaagga 300

aaatatgagg ggtggcaagg ttttgcctgt tacattctca aatggaagca aattagatat 360

gtcattg 367

<210> SEQ ID NO 77
<211> LENGTH: 257
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 77

actagnacag naattttagc taagtggagt ttgagttaag tggagatgtg agaccatctc 60

atagaaatca ttatttctgt gggatggata attgggccaa attgtaaaat attttaacta 120

tcagtgtttg gggtttattt ttaaaagaat agggtgccac cagatgttct ttagtggagg 180

agaaatgagg ccagagtgac tgcctagaaa attaagttgg taaattaatc actttttct 240

aggtcctttc ttagtct 257

<210> SEQ ID NO 78
<211> LENGTH: 373
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (61)..(62)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (66)..(66)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (83)..(84)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (109)..(109)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (115)..(115)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (146)..(146)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (153)..(153)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (166)..(166)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 78

ctttaaaaac ntgttagacn aacnttaaaa nttacccntt ttcctgaact gantcctggg 60

nntaantaaa aagggtgaag aannttactt cncttggtcc taaaaaacnt tttcntcagt 120

tattaccaaa atatttggac cattantaaa gantagggcc aacccnaatt tttcttgaaa 180

tttccgttaa atagccgtta aatgttttta cccatttcat attggatacc ttaaattata 240

ataatggatt ttattgttaa attgtgtgtg tgtggtgtgt atgccctgtc ttttctcctc 300

taccattatt gtcactttat gtttggaacc ccctttaccc ttccttaaag gaaaaaaagg 360

gcccggggtt ttt 373

<210> SEQ ID NO 79
<211> LENGTH: 128
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (29)..(30)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (35)..(35)

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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (92)..(92)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 79

tcctagtaan ctggtttacn ctgaaagann aagangcctc ccctgttcnc tgaaatacca 60

ccttgatgtt caagtattta agaccctatg cnaatatttt ttacctttc taataaacca 120

tgtttgtt 128

<210> SEQ ID NO 80
<211> LENGTH: 213
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (98)..(98)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (127)..(127)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (142)..(142)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (147)..(147)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (161)..(161)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (166)..(167)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (171)..(171)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (180)..(180)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (196)..(196)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (206)..(206)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 80

cccattggna cagacccca aaatgggtac atttttagg aaaccaggac ctttccaagg 60

ggccaggcct tccctttaaa aaaaaatnac cgtttttngg gggangnaac ctttaaaagg 120

ggaaaanaaa tccttttaa anggaantcc aagggaagga ncctgnncaa nacttccccn 180

ccaataaaaa aaaccntttt ggaaangggg aaa 213

<210> SEQ ID NO 81
<211> LENGTH: 443
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (22)..(22)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (33)..(34)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 81

gaaatgagat gaaaccatga gnatgaaatg aannaatgnc atgcaaatga tgagatgaaa 60

tgatgaaatg agatgagatg agaagaaatg acttgatgag atgagataaa atgatgaaat 120

gaaatgaagt gaaatgaaat tgaaatgaga tgagatgaaa tgagataaaa tgatgagatg 180

aaatgagaag aaatgagatg aaatgatgaa atgatgagat gagatgaaaa atgatgggat 240

gagaaatgag atgaaatgat gggatgaaat gaaatgaaat aatgaaataa tgaaatgaaa 300

tgaattgata atattgaagt gaaattgaaa gatgagattg gatgaaatga tgagatgaaa 360

tgaaatgttg aaatgaaatg aagagatgta acatgaaatg agctgaaatg atgagatgaa 420

atgaaatgaa atgagattaa atg 443

<210> SEQ ID NO 82
<211> LENGTH: 442
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (78)..(78)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (82)..(83)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (121)..(121)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 82

tggcccggga acntcnaact gcccatcctg gantttggg ggggannctt taaaaaacct 60

gacctctgaa tgtattantg anncaagtga tagccaagat attttgaaga aaaatagata 120

ntagggacct gctctataag cccatcataa tttattatga agttataaca agtaaaacag 180

taaggtattt ggcatggaat agagaaccca gaaacagacc caatgcatgg gtacaggata 240

taacacaggg aaatgaggga caatatatgg ttctgggata attatttata tggggaaaat 300

aaagaaattg gatccctacc tcacacatac aaaaaaaatc ataattgaat taaaaacttg 360

catgtgaaag gaaagacttt aaaacattta gaaaaagtat tggaggctat gatcttgggg 420

taggaaagca tttctttttt tt 442

<210> SEQ ID NO 83
<211> LENGTH: 135
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 83

gtctaacnta aaaagtaaag aaagtaaagt aaaggnttga aggaaggaag gaaggaagga 60

aggagggaaa agaaagaaag gaaggaagga aggaaaagaa agaaagaaag gaaggaagga 120

aggaaggaag gaagg 135

<210> SEQ ID NO 84
<211> LENGTH: 346
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 84

ggaggaggaa gagtgatgag ttctctaatn acttggttgg attagcctta gagttatcgg 60

gagttgcctt ctgtaagtgc ccctactatc aaggtttcat ggaaaatcta ggcaaggcag 120

aacttcctca gaaggacaag agacaaagaa gtgggggagg ccctcctatc catagctgag 180

agggtttatt ctttgtggtt ctgctgtcag agcctttgga tgtctgatct gagatggagc 240

aaccccagct agacagaact ttgtagattt tgggggttt aaaaggcctc aagcaaattc 300

taaaactttc tttgaacccc ctggcatagg ctcagtttcc ctgact 346

<210> SEQ ID NO 85
<211> LENGTH: 100
<212> TYPE: DNA

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<213> ORGANISM: Human

<400> SEQUENCE: 85

acaaaaagcc cctttaaact tgggcccgct cgaggtcgtt tcgactgggc cgagacttcc 60

gaaaagaaaa tggtttttt tgccgaaatc aaccgggtaa 100

<210> SEQ ID NO 86
<211> LENGTH: 201
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 86

ttcataacat cgtcattttg ggttatgcga aatacaaatt taaatctttg tgaaatgaaa 60

gaaaagagga agaaacgctt tttaggagtt aaggattaaa gtaaaaatta ttttgacata 120

attacctctt tttgtgacca ctcttaaagg ccaggaacat atttggagaa gcctagttgt 180

atgtaacagt gtggggtttc a 201

<210> SEQ ID NO 87
<211> LENGTH: 531
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 87

tatagcgggc gttataaaca taccacttcc cggtacaacg gatttcaagg ttaggggtgc 60

aacccagaac gaacgcgtta agtgcgcgtt atcttcctag gatagagtcg gtgacgggaa 120

tcttttaccc cggcactcgg gtccaccctc gcggcaccag aggtattctc cggcgagtcg 180

ttaaccatcg caatcgccga ccgagtttaa ggaccactcc ccacctttct cattagttaa 240

ggagaacgct actttacccc atagacggag aaatcgctac tcaactacca ggcgcgcgcc 300

gtcgagtccc tcttcctctc tttatgcatt tagagcgctt tcgtaagagt tttccctaga 360

ttcttctaag cgtagcgcgt ctactccaat gttttcgtta atccagcccg aactaacgcc 420

gcggaggagt cgatccgtct actcctatcc cgtcggctcg gatttactac aggagctaag 480

aaaacaaaaa gtaccagccc taaaggaaag tcaaaggacg cccgtaaaaa a 531

<210> SEQ ID NO 88
<211> LENGTH: 530
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 88

aatctcgatc gcaaacatac ggcactctcc ctcttgccgc ggttttcgtc cagcgctttc 60

cattcggtcc agtgcctcgc cctattagcc cttaagccca ccgtttctaa aactcccaga 120

acagccaaac cggtccgccc aaggcctccg tcgttttata atatattccg tttacgtata 180

aggaacgaac ccccccttcat taccacggtc ccgcgtccgc ctccttctcc attcgcaaca 240

gttctattcc tttcagcctc ccgtacctgc ttccagaaca tcgcaccgcc atagtcgaaa 300

gatagcaaag attacccagc ttctattcct cgccccagag ccgagtaaat cgaagtttat 360

agaggcggaa tccaaccatt caagagttat aacaagttat cggcactcgg gggatcagaa 420

tataaactta atgtcccctt tattctcccg gacgcccctt ttaaccactt cttcctatct 480

ttcgctaaca agccattgac ggcgctttgc cgcgcgggcc catctcgcgt 530

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<210> SEQ ID NO 89
<211> LENGTH: 332
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (47)..(47)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (112)..(112)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (129)..(129)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (134)..(134)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (152)..(152)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (168)..(168)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (196)..(196)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (239)..(239)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 89

ccatttatgg gccggggata tacccacatg gtacagnaca ttacatnttt atggcaccat 60

ttccaccggc ctggttttgg tttttccata attaattaac caggggggncc anttaaaaaa 120

aattaaggna aggnttaaaa aatttaacca angggggggtt taaagggntt ttttttttta 180

aaaaaaaagg ttaaancccc ccctttttttt ttgggttggg gtgggaaaat tttgggaanc 240

cttaaccccc gggtttttgg gttttttttgg ccaaaacccc ccggaaaaaa attaaaaaaa 300

ggaccggttt ccattttaat gggtattggg aa 332

<210> SEQ ID NO 90
<211> LENGTH: 185
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 90

actgctataa tgcaggggaa catgttctca gggtcatcct gaggggttgt gtcatggggc 60

cggtggtaac tattaaaaca taagtttaat cggtatttaa aattttaaaa tcaaaaaaaa 120

taaaatatat gcaaccctcc attccaagga agtatgatgt tactagatta tctgaaaatt 180

ctcct 185

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<210> SEQ ID NO 91
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (326)..(326)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (338)..(339)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (344)..(344)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 91

ccagagagcc acaaatgacc aaaatatttt gagatgaaca tgctcgtaga aggtagctga 60

ctaggggtga cttgaaaatg ctagaccagg ataactccta agtgtatatc cttggcagac 120

tcgttatgct ttccaatcct gcttgcaata taagacacaa agtcagaata aagctcaaga 180

aaacagaacg tgcaggccat caagcgcaga gcctgctcat tggacaaccg caaagagtag 240

taagtgctgc cgctattcac acttagaaaa ggagaaccac ggggaaaaac caaattaatg 300

gggctgcttt ttgtcactct ggcatnagag aattgtgnng aaantttaac ttttgtaagc 360

ttgta 365

<210> SEQ ID NO 92
<211> LENGTH: 113
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 92

acttgacctt atggatgatg ctgcggagtg cntngtaagt gtttcatgat attccttaag 60

aagtcaggat agtagttttc attccttaga tggtacaagt gttgagacaa atg 113

<210> SEQ ID NO 93
<211> LENGTH: 210
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 93

gttttaggga aatttgccag ttttatgttt taatattttt ggaaggaaaa ctgaaaggta 60

atgaaaatgt tactgttgga ttaaaaaaca aattaagtcc aaatagtgat taggcaagtt 120

ggtgaggtag ggggttgctg caagagcgga agttgaaaga tcttggaaaa attaaagaaa 180

cttcatagaa ccccatctct acaccaaaaa 210

<210> SEQ ID NO 94
<211> LENGTH: 506
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:

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<221> NAME/KEY: misc_feature
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naaannnggn nctnggggggg ggaaantttt ggccccccccc cgggggnttt ncctnaaaaa 240

aaanccnttt naaanacngn nanaattttn ccnnnncggg gaggngngga nnttttttttt 300

tnaannagcc ntttttgnna naaaaannnt ggnccccccc ctattccnng gntttngga 360

ccnttnnanc ntgggnnttt ttagnccttn aaaaaaangc naatnttaag gtaaaaattn 420

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ttttctctta tntgnngncn naacatctgc nngctctgnt annaanaatt ncataccgcn 240

canngtctnt gacgntgtga tgcatacgnt tgggcagagn gancaatang tgngcatatg 300

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<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
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<221> NAME/KEY: misc_feature
<222> LOCATION: (788)..(788)
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<220> FEATURE:
<221> NAME/KEY: misc_feature
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aaatgaaatg aaataatgaa atgaaattga aataaaattg aaatgagatg agatgaaatg 120

atgagatgat gaaataaaat gatgaaatga gatgtgatga gatgaaatga ngagatgaaa 180

tgatgagatg agatgacatg aaataaatga aataatgaaa tcgaaatgag atgagaagat 240

acgagatgag atgaaatgat gagatgaaat gatgaaatga gataagatga aaagagttga 300

tgagatgatg agatgaaatg agatgaaaag agatgaaatg agatgaaatg aaatgatgag 360

atgaaatgag gtgaaatgaa attagatgaa acgtaatgag atgaaatgac ataatgaaat 420

gaaaaaatga aatgaaataa tgaaatgagg tgaaattaaa tgagatgatg aaattaaatg 480

atgaaatgaa ataatgaaat ggaaatgaaa tggaaatgat gagatgaatg atgagatgaa 540

atgatgagat gagatgtatt gatgagagga aatgatgaga tgtaatgaaa tgagatgaaa 600

tgaatgagat gaaatggaat antggaangg aaattgattg gngatttgag atgaaatgag 660

ntaaatgnga tgaattaatg atgagatgaa atgntgaatg ccggggtgnn tgagatgaat 720

tgagttgaac cctgngatga atgaagattg nntgaatggt ggntgaatgt tgaatggntg 780

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gntggnanaa tgcctgtngg 800

<210> SEQ ID NO 97
<211> LENGTH: 334
<212> TYPE: DNA
<213> ORGANISM: Human

<400> SEQUENCE: 97

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atgaaatgat attgaaatga aattgaaaga tgagatgatg agatgaaatg gtgaaatgtt 120

gaaatgaaat gatgaaatga atagatgtga catgaaatga gctgaaatga tgagatcaaa 180

tgaaatgaaa tgagattaaa tgatgagatg aaaactgatg aaaacttaaa tgatgaaata 240

atgaaatgaa aatgaaatgg aaatgatgag atgagaagaa atgatgagat gagatgagat 300

aaaatgagat gaaatgatga gatgaaatga tgag 334

<210> SEQ ID NO 98
<211> LENGTH: 100
<212> TYPE: DNA
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<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 98

ttcaggccgt ctgcttntac atatactatc gagaatggtg ctgtgcactc ataacaccgt 60

tgcttggtag acgcttttga acccttcagc gctgaaagta 100

<210> SEQ ID NO 99
<211> LENGTH: 500
<212> TYPE: DNA
<213> ORGANISM: Human
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: n is a, c, g, or t

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gaaatgaaat gatgagatga aatgaggtga aatgaaatta gatgaaacgt aatgagatga 180

aatgacctaa tgaaatgaaa aaatgaaatg aaataatgaa atgaggtgaa attaaatgag 240

atgatgaaat taaatgatga aatgaaataa tgaaatggaa atgaaatgga aatgatgaga 300

tgaatgatga gatgaaatga tgagatgaga tctaatgatg agaggagatg atgagatgaa 360

ntgagatgaa aagagatgaa atgagatgaa accgaaatga tgagatgaaa tgaggtgaaa 420

tgaaattaga tgaaacgtaa tgagatgaaa tgacataatg aaatgaaaaa atgaaatgaa 480

ataatgaaat gaggtgaaat 500

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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (177)..(177)
<223> OTHER INFORMATION: n is a, c, g, or t

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tccccttgaa nntctctaaa ccttaacttt ctggccnttt tgtttcagan atgcctaacc 120

ctcagggggt cttttgttct ctacgcctaa aaacttaatc tgtttggaac aattccnttt 180

cctctctgta gaaattgacc tggccatggc tcctgtgaat gatacggttg ctattatccc 240

tgaacactgt aaaaatgaac tttgaaacag ttgggtagga cccaaacaga aaatgatgta 300

tggcttggaa atagtttagc tgaacattat gctttaatat tttactggcc attgcagcac 360

aggtttagaa atttatgttc ggctttttaa agtttta 397

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<212> TYPE: DNA
<213> ORGANISM: Human
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<222> LOCATION: (121)..(121)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 101

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attaattgta ctactttcaa aagaattaat tgaagaaaga gagatacagg gtatctaggc 120

ngaggaagac cc 132

<210> SEQ ID NO 102
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<212> TYPE: DNA
<213> ORGANISM: Human

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ggggggcttta gttataactg ggctaagcat aattgcgcta ccaattccat attatctcat 60

ggcacttaat tttataattg atatatataa taaaaaattc aatgcagata ttgatataat 120

aaaaatagat aatggtaatc caagcacgat ggtagccatc actctaattg ctttggggtt 180

aacctataac ttattaagta aagtgccaga atggttcttt gacagtatta aaattaaaga 240

aaacag 246

<210> SEQ ID NO 103
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<223> OTHER INFORMATION: forward primer of exon 1 of insulin gene used for quantitative RT-PCR analysis
<220> FEATURE:
<221> NAME/KEY: primer_bind
<222> LOCATION: (1)..(18)

<400> SEQUENCE: 103

gccctctggg gacctgac 18

<210> SEQ ID NO 104
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<223> OTHER INFORMATION: reverse primer of exons 1 and 2 of insulin gene used for quantitative RT-PCR analysis
<220> FEATURE:
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cccacctgca ggtcctct 18

<210> SEQ ID NO 105
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<223> OTHER INFORMATION: forward primer of beta-MyHC gene used for quantitative RT-PCR analysis
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<222> LOCATION: (1)..(24)

<400> SEQUENCE: 105

gctggaacgt agagactccc tgct 24

<210> SEQ ID NO 106
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<220> FEATURE:
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<400> SEQUENCE: 106

ggatccttcc agatcatcca cttg 24

<210> SEQ ID NO 107

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<211> LENGTH: 20
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<223> OTHER INFORMATION: forward primer of ANF used for quantitative RT-PCR analysis
<220> FEATURE:
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<222> LOCATION: (1)..(20)

<400> SEQUENCE: 107

ggatttcaag aatttgctgg 20

<210> SEQ ID NO 108
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: reverse primer of ANF used for quantitative RT-PCR analysis
<220> FEATURE:
<221> NAME/KEY: primer_bind
<222> LOCATION: (1)..(20)

<400> SEQUENCE: 108

gcagatcgat cagaggagtc 20

<210> SEQ ID NO 109
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<223> OTHER INFORMATION: forward primer of APP used for quantitative RT-PCR analysis
<220> FEATURE:
<221> NAME/KEY: primer_bind
<222> LOCATION: (1)..(20)

<400> SEQUENCE: 109

ggatgcttca tgtgaacgtg 20

<210> SEQ ID NO 110
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: reverse primer of APP used for quantitative RT-PCR analysis
<220> FEATURE:
<221> NAME/KEY: primer_bind
<222> LOCATION: (1)..(19)

<400> SEQUENCE: 110

tcattcacac cagcacatg 19

<210> SEQ ID NO 111
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: forward primer of ZFP used for quantitative RT-PCR analysis
<220> FEATURE:
<221> NAME/KEY: primer_bind
<222> LOCATION: (1)..(21)

<400> SEQUENCE: 111

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cacargagrc arggtcaacg a 21

<210> SEQ ID NO 112
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: reverse primer of ZFP used for quantitative RT-PCR analysis
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<221> NAME/KEY: primer_bind
<222> LOCATION: (1)..(22)

<400> SEQUENCE: 112

ggattaaaat gaagcaccca ga 22

**1**. A method of diagnosing or prognosing a disease in an individual, comprising the steps of:

a) determining the level of expression of a gene in a blood sample of an individual, and

b) detecting a difference of said level of expression of said gene in said blood sample according to step a) relative to the level of expression of the same gene of a control, wherein a difference in expression levels is indicative or predictive of said disease.

**2-18**. (canceled)

**19**. A method of identifying potential markers for differentiating between different body states, the method comprising:

for each gene of a set of two or more predetermined genes,

(a) determining a level of RNA encoded by the gene in whole blood samples of human subjects having a first body state, the level indicating expression of the gene in the samples; and

(b) comparing the level of step (a) with a level of RNA encoded by the gene in whole blood samples of human subjects having a second body state, the second state being different from the first state, the level in the samples of the subjects having the second state indicating expression of the gene in the samples of the subjects having the second state,

wherein a determination, resulting from step (b), of a significant difference between the levels identifies the gene as a potential marker for differentiating between the first state and the second state,

thereby identifying potential markers for differentiating between different body states.

**20**. The method of claim **19**, wherein determining the level of step (a) is done using at least one oligonucleotide of predetermined sequence.

**21**. The method of claim **20**, wherein determining the level of step (a) is done by amplifying RNA encoded by the gene using at least one primer to form amplified product, and quantifying the amplified product, wherein the at least one oligonucleotide comprises the at least one primer.

**22**. The method of claim **20**, wherein determining the level of step (a) is effected by hybridizing DNA complementary to RNA encoded by the gene with at least one probe to form hybridization product, and quantifying the hybridization product, wherein the at least one oligonucleotide comprises the at least one probe.

**23**. The method of claim **19**, wherein the subjects having the first state have a disease

**24**. The method of claim **23**, wherein the disease is colorectal cancer.

**25**. The method of claim **23**, wherein the disease is diabetes.

**26**. The method of claim **23**, wherein the disease is heart failure.

**27**. The method of claim **23**, wherein the subjects having the second state are healthy.

**28**. The method of claim **23**, wherein the subjects having the second state have the disease at a different stage than the subjects having the first state.

**29**. The method of claim **23**, wherein the difference is that the level of step (a) is lower than the level in the samples of the subjects having the second state.

**30**. The method of claim **19**, further comprising, prior to step (b), determining a level of RNA encoded by the gene in whole blood samples of human subjects having the second body state, thereby providing the level of RNA encoded by the gene in whole blood samples of human subjects having the second body state.

**31**. The method of claim **30**, wherein determining the level of step (a) and determining the level in samples of subjects having the second state is done using at least one oligonucleotide of predetermined sequence.

**32**. The method of claim **31**, wherein determining the level of step (a) and determining the level in samples of subjects having the second state is done by amplifying RNA encoded by the gene using at least one primer to form amplified product, and quantifying the amplified product, wherein the at least one oligonucleotide comprises the at least one primer.

**33**. The method of claim **31**, wherein determining the level of step (a) and determining the level in samples of subjects having the second state is effected by hybridizing DNA complementary to RNA encoded by the gene with at least one probe to form hybridization product, and quantifying the hybridization product, wherein the at least one oligonucleotide comprises the at least one probe.

**34**. The method of claim **30**, wherein the subjects having the first state have a disease.

**35**. The method of claim **34**, wherein the disease is colorectal cancer.

**36**. The method of claim **34**, wherein the disease is diabetes.

**37**. The method of claim **34**, wherein the disease is heart failure.

* * * * *

| | | | |
|---|---|---|---|
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| [标]发明人 | LIEW CHOONG CHIN | | |
| 发明人 | LIEW, CHOONG-CHIN | | |
| IPC分类号 | C12Q1/68 G01N33/53 | | |
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| 外部链接 | Espacenet USPTO | | |


摘要(译)

本发明涉及检测和测量基因转录物及其在血液中的等同核酸产物。具体提供了对一滴血进行的分析，用于使用基因特异性和/或组织特异性引物检测，诊断和监测疾病。本发明还描述了通过其描绘疾病特异性基因的表达水平的序列和/或定量的方法，其允许对疾病进行即时和准确的诊断/预后测试或评估特定治疗方案的效果。


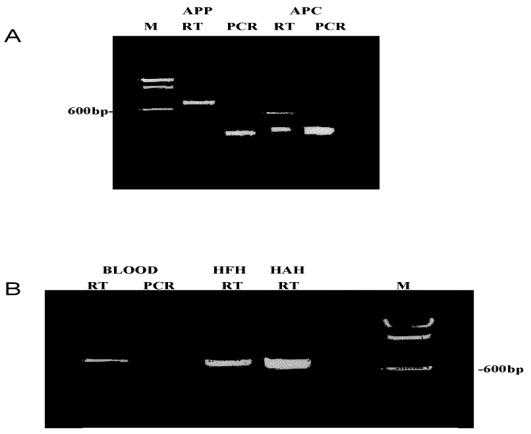


Figure 1