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(71) Applicants:
- **FUJIKURA KASEI CO., LTD.**
  Itabashi-ku
  Tokyo 174-0046 (JP)
- **National University Corporation Chiba University**
  Chiba-shi
  Chiba 263-8522 (JP)

(72) Inventors:
- **NAKAMURA Rika**
  Saitama 3400203 (JP)
- **KURODA Hideyuki**
  Saitama 3400203 (JP)
- **TOMIYOSHI Go**
  Saitama 3400203 (JP)
- **HIWASA Takaki**
  Chiba-shi
  Chiba 260-8670 (JP)
- **TAKIGUCHI Masaki**
  Chiba-shi
  Chiba 260-8670 (JP)
- **SAEKI Naokatsu**
  Chiba-shi
  Chiba 260-8670 (JP)
- **MACHIDA Toshio**
  Chiba-shi
  Chiba 260-8670 (JP)

(74) Representative: **Wright, Andrew John et al**
Potter Clarkson LLP
Park View House
58 The Ropewalk
Nottingham NG1 5DD (GB)

(54) POLYPEPTIDE MARKER FOR DIAGNOSIS OF ARTERIOSCLEROSIS, METHOD FOR DETECTION OF ARTERIOSCLEROSIS BY USING THE MAKER OR THE LIKE, AND KIT FOR DIAGNOSIS OF ARTERIOSCLEROSIS

(57) Disclosed are: a polypeptide marker for diagnosing arteriosclerosis; a gene marker for diagnosing arteriosclerosis; an antibody; a probe for detecting an arteriosclerosis marker gene; a DNA microarray or a DNA chip for detecting an arteriosclerosis marker gene; a method for detecting arteriosclerosis; and a kit for diagnosing arteriosclerosis; with which an arteriosclerotic lesion can be detected with much improved accuracy. Specifically disclosed are: a polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 of the Sequence Listing, or a partial amino acid sequence thereof; a gene which encodes the amino acid sequence; a probe for detecting the gene; a DNA microarray or a DNA chip comprising the probe; an antibody bindable to the polypeptide as an antigen; a kit comprising any one of the above-mentioned items; and a method for detecting arteriosclerosis by using any one of the above-mentioned items.

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Description

TECHNICAL FIELD

[0001] The present invention relates to polypeptide markers for diagnosing arteriosclerosis, gene markers for diagnosing arteriosclerosis, antibodies, probes for detecting an arteriosclerosis marker gene, a DNA microarray or a DNA chip for detecting the arteriosclerosis marker genes, a method for detecting arteriosclerosis, and a kit for diagnosing arteriosclerosis.
Priority is claimed on Japanese Patent Application No. 2008-209210, filed August 15, 2008, the content of which is incorporated herein by reference.

BACKGROUND ART

[0002] Arteriosclerosis is a disease frequently found in aorta, coronary arteries, cerebral arteries, and carotid arteries, being a main cause of myocardial infarction and cerebral infarction. At present, the presence of atherosclerosis is said to be crucial for the ground of the onset of ischemic organ diseases such as ischemic heart disease and cerebrovascular disorder, which are top leading causes of death. Arteriosclerotic lesions are pathomorphologically characterized by: fatty streaks which are subendothelial accumulations of cholesterol ester-storing cells (foam cells); and as an advanced stage thereof, invasions of smooth muscle cells, macrophages, T cells, and the like; as well as fibrous plaques showing cellular necrosis and fat accumulation. The site with fat accumulation is structurally fragile, where plaques are ruptured, triggered by a hemodynamic force, and thereby a thrombus is rapidly formed by reactions of tissue factors and blood coagulation factors. It has been elucidated that the occurrence of thrombotic blockage by the rupture of plaques in a coronary artery is closely associated with the onset of so-called acute coronary syndromes such as acute myocardial infarction, unstable angina pectoris, and cardiac sudden death (Non-Patent Document 1)

[0003] Arteriosclerosis is gradually developed without subjective symptoms, and all of the sudden, myocardial infarction, cerebral infarction, or angina pectoris occurs. Thus, early stage detection is required. So far, ultrasonography, angiography, imaging tests with MRI (magnetic resonance imaging devices) or such a device, electrocardiography, electroencephalography, and the like have been widely carried out for the diagnosis of arteriosclerotic lesions. However, methods by means of biochemical examination have been demanded so that diagnosis of an arteriosclerotic lesion can achieve an early detection.

[0004] In the diagnosis of an arteriosclerotic lesion by means of biochemical examination, there has been known measurements of arteriosclerosis-induced lipoproteins which are associated with lipid accumulation in the vascular wall such as LDL (low density lipoprotein), lipoprotein (Lp-α), remnant lipoprotein, and oxidized LDL in serum or plasma. In particular, measurement of arteriosclerosis-associated substances in blood are attracting attention in recent years. It is reported that measurement of an inflammatory substance: CRP (C-reactive protein), and measurement of the chlamydia antibody titer are useful.

[0005] As for the diagnosis method of an arteriosclerotic lesion by means of such measurement of an arteriosclerosis-induced lipoprotein, the following methods are known. For example, regarding the LDL measurement, the followings have been proposed: measurement of neutrophil, monocyte/ macrophage or like inflammatory cell-originated components such as lactoferrin, myeloperoxidase, granulocytic elastase in serum or plasma, forming a complex with the oxidized LDL existing in the serum or the plasma, by an immunological means (Patent Document 1); use of an immunoassay method with a fused polypeptide comprising the extracellular region of an oxidized LDL receptor and a part of the heavy chain constant region of an immunoglobulin (Patent Document 2); use of an anti-human aldehyde-modified α1 antitrypsin monoclonal antibody capable of specifically recognizing oxidized LDL-α1 antitrypsin complex (Patent Documents 3 and 4); measurement of the degree of oxidative denaturation of LDL in plasma by an oxidizing agent comprising an azo compound such as V-70 (Patent Document 5); and the like.

[0006] Furthermore, regarding the diagnosis of an arteriosclerotic lesion by means of lipoprotein measurement, the followings have been disclosed: measurement of remnant lipoprotein (RLP) in denatured blood (Patent Document 6); diagnosis of rheumatoid or arteriosclerotic lesions through detection of the expression of the human cartilage GP39-L polypeptide gene (Patent Document 7); diagnosis of arteriosclerotic lesions through measurement of apoB100 lipoprotein in blood (Patent Document 8); measurement of human phospholipid transfer protein (PLTP) with use of a monoclonal antibody against PLTP (Patent Document 9); use of an apo lipoprotein A-I antibody as a marker for diagnosing arteriosclerosis (Patent Document 10); and the like.

[0007] In addition, regarding other means related to the diagnosis of an arteriosclerotic lesion, the followings have been proposed: diagnosis of hyperlipemia or arteriosclerotic lesions with use of an antibody against a sodium dependent bile acid transporter protein (Patent Document 11); diagnosis through measurement of the coagulation factor VII-activating protease (FSAP) as a risk factor for atherosclerosis (Patent Document 12); examination of arteriosclerosis through detection of an endothelial and smooth muscle cell-derived neuropilin-like molecule (ESDN) or the gene expression

thereof (Patent Document 13); use of an anti-human hepatic triglyceride lipase antibody (Patent Document 14); diagnosis of arteriosclerotic lesions by using the serotonin concentration in a plasma sample as a marker (Patent Documents 15 and 16); and the like.

[0008] Furthermore, regarding yet other means related to the diagnosis of an arteriosclerotic lesion, the followings have been proposed: diagnosis of chronic renal failure or atherosclerosis by using, as the analyte, an sMAD3 polypeptide which is an iso-form of MAD required for the signal transduction of DPP which is a TGF-family member of cytokine/growth factor (Patent Document 17); measurement of a complex of Lp-α and α2-macroglobulin/interleukin 6 in blood as the analyte by an immunological means using an antibody thereof (Patent Document 18); use of a monoclonal antibody against a paraoxonase (Patent Document 19); detection of arteriosclerosis through measurement of a saturated ultra long-chain fatty acid (Patent Document 20); diagnosis of atherosclerosis by using an RC-9 protein and an antibody thereof (Patent Document 21); and the like.

In this way, many methods have been proposed regarding the biochemical examination related to the diagnosis of an arteriosclerotic lesion. However, most of the detection markers of them are risk markers. For more radical and specific diagnosis of an arteriosclerotic lesion, an advanced development of markers capable of specifically detecting such a lesion has been demanded.

[0009] Therefore, Patent Document 22 has proposed, as a marker for specifically detecting an arteriosclerotic lesion, a polypeptide marker for diagnosing arteriosclerosis, a gene marker for diagnosing arteriosclerosis, an antibody specifically bindable to the polypeptide marker for diagnosing arteriosclerosis, a probe for detecting the gene marker for diagnosing arteriosclerosis, and a method for detecting an arteriosclerotic lesion.

[0010]

Patent Document 1: Japanese Unexamined Patent Application, First Publication No. 2002-48790
Patent Document 2: Japanese Unexamined Patent Application, First Publication No. 2002-17353
Patent Document 3: Japanese Unexamined Patent Application, First Publication No. 2000-184885
Patent Document 4: Japanese Unexamined Patent Application, First Publication No. H10-142226
Patent Document 5: Japanese Unexamined Patent Application, First Publication No. H9-203736
Patent Document 6: Japanese Unexamined Patent Application, First Publication No. 2002-181820
Patent Document 7: Japanese Unexamined Patent Application, First Publication No. 2002-142781
Patent Document 8: Japanese Unexamined Patent Application, First Publication No. 2002-55106
Patent Document 9: Japanese Unexamined Patent Application, First Publication No. H11-346782
Patent Document 10: Japanese Unexamined Patent Application, First Publication No. H8-160042
Patent Document 11: Japanese Unexamined Patent Application, First Publication No. 2003-310281
Patent Document 12: Japanese Unexamined Patent Application, First Publication No. 2003-304873
Patent Document 13: Japanese Unexamined Patent Application, First Publication No. 2003-189872
Patent Document 14: Japanese Unexamined Patent Application, First Publication No. 2002-308900
Patent Document 15: Japanese Unexamined Patent Application, First Publication No. 2002-277461
Patent Document 16: Japanese Unexamined Patent Application, First Publication No. 2002-131313
Patent Document 17: Japanese Unexamined Patent Application, First Publication No. 2002-238589
Patent Document 18: Japanese Unexamined Patent Application, First Publication No. 2001-249128
Patent Document 19: Japanese Unexamined Patent Application, First Publication No. 2000-333674
Patent Document 20: Japanese Unexamined Patent Application, First Publication No. 2000-206113
Patent Document 21: Published Japanese translation No. 2000-503764 of PCT International Publication
Patent Document 22: Japanese Unexamined Patent Application, First Publication No. 2005-168498

[0011]

Non-Patent Document 1: N. Eng. J. Med., 326, 242-250, 1992.
Non-Patent Document 2: Journal of Biological Chemistry, 272, 556, 1997.

[0012] According to the technique of Patent Document 22, an arteriosclerotic lesion can be detected with easy manipulation, and an early detection of arteriosclerosis can be expected. However, it does not satisfy an adequate level. There has been a demand for more accurate detection of an arteriosclerotic lesion with use of a greater number of polypeptide markers for diagnosing arteriosclerosis, gene markers for diagnosing arteriosclerosis, and the like.

Therefore, it is an object of the present invention to provide polypeptide markers for diagnosing arteriosclerosis, gene markers for diagnosing arteriosclerosis, antibodies, probes for detecting an arteriosclerosis marker gene, a DNA microarray or a DNA chip for detecting an arteriosclerosis marker gene, a method for detecting arteriosclerosis, and a kit for diagnosing arteriosclerosis, with which an arteriosclerotic lesion can be detected with much improved accuracy.

DISCLOSURE OF INVENTION

[0013] The inventors of the present invention have searched for proteins which are expressed in serum of a diseased patient with an arteriosclerotic lesion so as to find out more markers for diagnosing arteriosclerosis which can specifically detect an arteriosclerotic lesion. As a result, they found out novel polypeptide markers for diagnosing arteriosclerosis which can specifically detect an arteriosclerotic lesion, which has led to the completion of the present invention.
In the specific search method, the screening was conducted in the following manner by using serum of diseased patients with arteriosclerotic lesions who had been hospitalized in a hospital or cooperative institutes with the consent of patients or their families. The obtained cDNA clone was inserted in a plasmid pBluescript II to determine the nucleotide sequence. Thereafter, it was recombined in a pGEX plasmid and transfected in *E. coli.* The protein was abundantly expressed with IPTG (isopropyl β-D-thiogalactoside) to thereby prepare the protein extract. Next, the protein extract was solid-phased in a 96-well plate. The antibody level in the serum was measured by the ELISA method. Using these measured values, a significance test was conducted between the arteriosclerosis patient group and the normal group. As a result, significant differences were found between the patient group and the normal group with thirteen clones serving as the marker of the present invention. Furthermore, the reaction between the protein extract and a large number of patient serums was examined by the western blotting method. As a result, five clones serving as the marker of the present invention newly exhibited a positive reaction with the serums of diseased patients with arteriosclerotic lesion, by which these five clones were found to be useful as specific markers for the presence of an arteriosclerotic lesion, or for an unstable plaque. Then, it became possible by utilizing the antigenicity of these clones or probes for these genes, to develop a method for detecting arteriosclerosis, and moreover to produce a diagnosis kit for use in such a detection method.

[0014] That is, the present invention includes polypeptide markers for diagnosing arteriosclerosis, gene markers for diagnosing arteriosclerosis, antibodies, probes for detecting an arteriosclerosis marker gene, a DNA microarray or a DNA chip for detecting an arteriosclerosis marker gene, a method for detecting arteriosclerosis, and a kit for diagnosing arteriosclerosis, which are described below.

[0015]

[1] A polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 1,3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 of the Sequence Listing, or a partial amino acid sequence thereof.
[2] A gene marker for diagnosing arteriosclerosis, which comprises a gene represented by a nucleotide sequence that encodes the amino acid sequence of the polypeptide marker for diagnosing arteriosclerosis according to [1], or a partial amino acid sequence thereof.
[3] A gene marker for diagnosing arteriosclerosis, which comprises a gene having a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10,12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing, or a partial nucleotide sequence thereof.

[0016]

[4] An antibody specifically bindable to the polypeptide according to [1] as an antigen.

[0017]

[5] A probe for detecting an arteriosclerosis marker gene, which comprises all or a part of DNA that is hybridizable with the gene according to [2] or [3] under a stringent condition.
[6] The probe for detecting an arteriosclerosis marker gene according to [5], which comprises all or a part of antisense DNA for the gene according to [3].

[0018]

[7] A DNA microarray or a DNA chip for detecting an arteriosclerosis marker gene, wherein the probe for detecting an arteriosclerosis marker gene according to [5] and/or the probe for detecting an arteriosclerosis marker gene according to [6] is/are immobilized on a base plate.

[0019]

[8] A method for detecting arteriosclerosis, wherein the antibody according to [4] is used to detect the expression of an arteriosclerosis marker polypeptide that is specifically bindable to the antibody, in a specimen sample.
[9] A method for detecting arteriosclerosis, wherein the polypeptide marker for diagnosing arteriosclerosis according

to [1] is used to detect the expression of an antibody that is specifically bindable to the polypeptide marker for diagnosing arteriosclerosis, in specimen blood.

[10] A method for detecting arteriosclerosis, wherein the probe for detecting an arteriosclerosis marker gene according to [5] or [6] is used to detect the expression of a gene that is hybridizable with the probe for detecting an arteriosclerosis marker gene, in a specimen cell.

[0020]

[11] A method for detecting arteriosclerosis, wherein a primer is constructed based on a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing, and PCR is conducted with use of the primer to detect the expression of an arteriosclerosis marker gene.

[12] A kit for diagnosing arteriosclerosis, including at least one item selected from the group consisting of the probe for detecting an arteriosclerosis marker gene according to [5] or [6], the DNA microarray or the DNA chip for detecting an arteriosclerosis marker gene according to [7], and the antibody according to [4].

[0021]

[13] A kit for diagnosing arteriosclerosis, including a polypeptide marker for diagnosing arteriosclerosis which comprises a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 of the Sequence Listing, or a partial amino acid sequence thereof.

[0022] An arteriosclerotic lesion can be detected with much higher accuracy by using the polypeptide marker for diagnosing arteriosclerosis, the gene marker for diagnosing arteriosclerosis, the antibody, the probe for detecting an arteriosclerosis marker gene, the DNA microarray or the DNA chip for detecting an arteriosclerosis marker gene, the method for detecting arteriosclerosis, and the kit for diagnosing arteriosclerosis of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 shows the results of the expression of arteriosclerosis marker genes by the western blotting method in the Examples.

DESCRIPTION OF EMBODIMENTS

[0024] The polypeptide marker for diagnosing arteriosclerosis and the gene marker for diagnosing arteriosclerosis of the present invention can be used for the detection of arteriosclerosis as they are specifically expressed in arteriosclerotic lesions. Polypeptides serving as the polypeptide marker for diagnosing arteriosclerosis of the present invention are polypeptides having an amino acid sequence set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 29 of the Sequence Listing, or a partial amino acid sequence thereof.

Here, the term "partial amino acid sequence" refers to a sequence being a part of the amino acid sequence set forth in any one of SEQ ID NOs of the Sequence Listing mentioned above, consisting of four or more, preferably five or more, more preferably six or more, and yet more preferably seven or more amino acids.

[0025] The information on the amino acid sequences of the above-mentioned polypeptides of the present invention are available from the NCBI GeneBank database as of July 31st, 2008, with the accession numbers: XM_001129783 (SEQ ID NO: 1), NM_006088 (SEQ ID NO: 3), NM_014878 (SEQ ID NO: 5), NM_207514 (SEQ ID NO: 7), NM_001128847 (SEQ ID NO: 9), NM_001017408 (SEQ ID NO: 11), NM_015089 (SEQ ID NO: 13), NM_133337 (SEQ ID NO: 15), NM_022406 (SEQ ID NO: 17), NM_001402 (SEQ ID NO: 19), NM_005349 (SEQ ID NO: 21), NM_005406 (SEQ ID NO: 23), NM_016436 (SEQ ID NO: 25), NM_032408 (SEQ ID NO: 27), and NM_014377 (SEQ ID NO: 29).

[0026] In addition, the gene marker for diagnosing arteriosclerosis of the present invention comprises a gene represented by a nucleotide sequence which encodes the above-mentioned polypeptide having the amino acid sequence or a partial amino acid sequence thereof. The gene marker for diagnosing arteriosclerosis may be a gene having a nucleotide sequence capable of expressing the above-mentioned polypeptide.

[0027] The gene serving as the gene marker for diagnosing arteriosclerosis of the present invention can be exemplified by genes of the following clones, as well as being genes having a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing, or a partial nucleotide sequence thereof. The information on these genes (nucleotide sequence information) are respectively available from the NCBI GeneBank database, with the following accession numbers.

[0028] That is, the gene serving as the gene marker for diagnosing arteriosclerosis can be exemplified by [Clone Name: S 19A3; SEQ ID NO: 2 of the Sequence Listing; Accession No. XM_001129783; Gene Name: (PREDICTED)

similar to LIM and senescent domain 1 (LOC729260); Gene Description: similar to the LIMS 1 gene. LIMS 1 is an adaptor protein which contains five LIM domains, or double zinc fingers. LIMS 1 may possibly play a role in integrin-mediated cell adhesion or spreading.], [Clone Name: TS27A2; SEQ ID NO: 4 of the Sequence Listing; Accession No. NM_006088; Gene Name: tubulin, beta 2C (TUBB2C); Gene Description: a component protein of microtubules], [Clone Name: S21 B 1; SEQ ID NO: 6 of the Sequence Listing; Accession No. NM_014878; Gene Name: KIAA0020 (KIAA0020); Gene Description; reportedly a minor histocompatibility antigen], [Clone Name: S25E1; SEQ ID NO: 8 of the Sequence Listing; Accession No. NM_207514; Gene Name: differentially expressed in FDCP 8 homolog (mouse) (DEF8); Gene Description: unknown function], [Clone Name: TS12D2; SEQ ID NO: 10 of the Sequence Listing; Accession No. NM_001128847; Gene Name: SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4); Gene Description: unknown], [Clone Name: S36C3; SEQ ID NO: 12 of the Sequence Listing; Accession No. NM_001017408; Gene Name: golgi associated PDZ and coiled-coil motif containing (GOPC); Gene Description: bindable to Rhotekin, an effector of a low molecular weight GTP-binding protein Rho. Moreover, reportedly, the binding between Rhotekin and GOPC is regulated in a Rho dependent manner.], [Clone Name: N48B1; SEQ ID NO: 14 of the Sequence Listing; Accession No. NM_015089; Gene Name: p53-associated parkin-like cytoplasmic protein (PARC); Gene Description: associated with transition from metaphase to anaphase during cell division, and also associated with ubiquitin-dependent protein degradation], [Clone Name: S28D1; SEQ ID NO: 16 of the Sequence Listing; Accession No. NM_133337; Gene Name: fer-1-like 3, myoferlin (C. *elegans)* (FER1L3); Gene Description: a type II membrane protein similar to a skeletal muscle protein, dysferlin, this gene having a C2 domain is suggested to be possibly associated with regeneration and repair of cytoplasmic membrane and nuclear membrane], [Clone Name: TS27H1; SEQ ID NO: 18 of the Sequence Listing; Accession No. NM_022406; Gene Name: X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4); Gene Description: a protein encoded by this gene acts to complete the repair of a DNA double strand through nonhomologous end joining and V(D)J recombination, together with DNA ligase IV and DNA-dependent protein kinase. The nonhomologous end-joining pathway is necessary for the normal development and suppression on tumors.], [Clone Name: PA105; SEQ ID NO: 20 of the Sequence Listing; Accession No. NM_031229; Gene Name: RanBP-type and C3HC4-type zinc finger containing 1 (RBCK1); Gene Description: unknown function. Its amino acid sequence is similar to that of mouse UIP28/UbcM4 interacting protein], [Clone Name: S16D2; SEQ ID NO: 22 of the Sequence Listing; Accession No. NM_005349; Gene Name: recombination signal binding protein for immunoglobulin kappa J region (RBPJ); Gene Description: unknown], [Clone Name: S27D3; SEQ ID NO: 24 of the Sequence Listing; Accession No. NM_005406; Gene Name: Rho-associated, coiled-coil containing protein kinase 1 (ROCK1); Gene Description: serine/threonine kinase activated by a low molecular weight GTP-binding protein Rho, and associated not only with cell contraction but also with morphological regulation, migration, regulation of gene expression, and like physiological functions.], [Clone Name: S36E1; SEQ ID NO: 26 of the Sequence Listing; Accession No. NM_016436; Gene Name: PHD finger protein 20 (PHF20); Gene Description: associated with DNA-dependent transcriptional regulation.], [Clone Name: S39D6; SEQ ID NO: 28 of the Sequence Listing; Accession No. NM_032408; Gene Name: bromodomain adjacent to zinc finger domain, 1B (BAZ1B); Gene Description: a member of the bromodomain protein family involved in chromatin-dependent regulation of transcription.], [Clone Name: TS27B2; SEQ ID NO: 30 of the Sequence Listing; Accession No. NM_014377; Gene Name: zuotin related factor 1 (ZRF1); Gene Description: a member of the M-phase phosphoprotein family, acting as a molecular chaperone.], [Clone Name: PA202; SEQ ID NO: 32 of the Sequence Listing; Accession No. NM_003692; Gene Name: transmembrane protein with EGF-like and two follistatin-like domains 1 (TMEFF1); Gene Description: reportedly inhibits nodal signaling through binding to the nodal coreceptor Cripto in *Xenopus],* [Clone Name: PA213; SEQ ID NO: 34 of the Sequence Listing; Accession No. NM_006807; Gene Name: chromobox homolog 1 (HP1 beta homolog *Drosophila)* (CBX1); Gene Description: localized at heterochromatin sites, where it mediates gene silencing.], [Clone Name: PA234; SEQ ID NO: 36 of the Sequence Listing; Accession No. BC030642; Gene Name: PARK2 co-regulated (PACRG); Gene Description: Parkinson's disease-associated gene, and reportedly regulated by the ubiquitin-proteasome system.].

In addition, the term "partial nucleotide sequence" refers to a sequence being a part of the nucleotide sequence set forth in any one of SEQ ID NOs of the Sequence Listing mentioned above, consisting of twelve or more, preferably fifteen or more, more preferably eighteen or more, and yet more preferably twenty or more nucleotides (hereunder, the same definition will be applied).

The above-mentioned genes serving as the gene marker for diagnosing arteriosclerosis are summarized in Table 1.

[0029]

[Table 1]

	Clone Name	SEQ ID NO.	Accession No.	Gene Name
1	S19A3	2	XM_001129783	(PREDICTED similar to UM and senescent domain 1 (L00729260)

(continued)

	Clone Name	SEQ ID NO.	Accession No.	Gene Name
2	TS27A2	4	NM_006088	tubulin, beta 2C (TUBB2C)
3	S21B1	6	NM_014878	KIAA0020 (KIAA0020)
4	S25E1	8	NM_207514	differentially expressed in FDCP 8 homolog (mouse) (DEF8)
5	TS12D2	10	NM_001128847	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4)
6	S36C3	12	NM_001017408	golgi associated PDZ and coiled-coil motif containing (GOPC)
7	N48B1	14	NM_015089	p53-associated parkin-like cytoplasmic protein (PARC)
8	S28D1	16	NM_133337	fer-1-like 3, myoferlin (C. elegans) (FER1 L3)
9	TS27H1	18	NM_022406	X-ray repair complementing defective repair in Chinese hamster celts 4 (XRCC4)
10	PA105	20	NM_001229	RanBP-type and C3HC4-type zinc finger containing 1 (RBCK1)
11	S16D2	22	NM_005349	recombinations signal binding protein for immunoglobulin kappa J region (RBPJ)
12	S27D3	24	NM_005406	Rho-associated, coiled-coil containing protein kinase 1 (ROCK1)
13	S36E1	26	NM_016436	PHD finger protein 20 (PHF20)
14	S39D6	28	NM_ 032408	bromodomain adjacent to zinc finger domain, 1B (BAZ1B)
15	TS27B2	30	NM_014377	zuotin related factor 1 (ZRF1)
16	PA202	32	NM_003692	transmembrane protein with EGF-like and two follistatin-like domains 1 (TMEFF1)
17	PA213	34	NM_006807	chromobox homolog 1 (HP1 beta homolog Drosophila) (CBX1)
18	PA234	36	BC030642	PARK2 co-regulated (PACRG)

[0030] The antibody of the present invention is an antibody specifically bindable to, as an antigen, a polypeptide serving as the above-mentioned polypeptide marker for diagnosing arteriosclerosis. The antibody may be either monoclonal or polyclonal. These antibodies can be produced by a usual method using the above-mentioned polypeptide as an antigen.

[0031] The antibody of the present invention may be labeled with a labeling substance. As for the labeling substance, it is possible to use an enzyme, a radioisotope, a fluorescent dye, biotin, digoxigenin, or the like. The enzyme is not specifically limited as long as it fulfills the requirements such as a large turnover number (number of revolution), stability in the antibody-binding state, and capability of rendering the substrate a specific color. For example, peroxidases for use in usual EIA (enzyme immunoassay), β-galactosidase, alkaline phosphatase, glucose oxidase, acetylcholine esterase, glucose-6-phosphate dehydrogenase, malate dehydrogenase, or the like can be used. In addition, it is also possible to use an enzyme inhibitory substance, a coenzyme, or the like. These enzymes can be bound to the antibody by a known method using a maleimide compound or such a crosslinking agent.

As for the substrate, it is possible to use a known substance according to the type of the enzyme to be used. For example, 3,3',5,5'-tetramethylbenzidine can be used as a substrate when peroxidase is used as an enzyme, while paranitrophenol can be used as a substrate when alkaline phosphatase is used as an enzyme.

[0032] As for the radioisotope, it is possible to use ^{125}I, ^{3}H, or such a substance for use in usual RIA (radioimmunoassay).

As for the fluorescent dye, it is possible to use fluorescein isothiocianate (FITC), tetramethylrhodamine isothiocyanate (TRITC), or such a substance for use in usual fluorescence antibody technique.

[0033] In addition, these labeled antibodies may be tagged with a metal such as manganese or iron. By administering such a metal-tagged antibody into the body and assaying the metal by MRI or such a means, the presence of an antigen peptide bound to this antibody (a polypeptide marker for diagnosing arteriosclerosis) can be detected.

[0034] In addition, the probe for detecting an arteriosclerosis marker gene of the present invention is a probe which comprises all or a part of DNA that is hybridizable with the gene serving as the gene marker for diagnosing arteriosclerosis mentioned above under a stringent condition. Here, the term "stringent condition" of the present invention can be exemplified by: hybridization in a buffer solution containing 50% formamide, 5×SSC, 5×Denhardt's solution, 0.1M sodium dihydrogenphosphate (pH6.5); 0.5% SDS, and 100 μg/ml denatured salmon sperm DNA, at 42°C, followed by a washing treatment in a buffer solution containing 1×SSC (0.15M NaCl and 0.015M sodium citrate) and 0.1% SDS (sodium dodecyl sulfate) at 42°C (Condition 1); or, hybridization in a buffer solution containing 5×SSC, 5×Denhardt's solution, 0.1M sodium dihydrogenphosphate (pH6.5), 0.5% SDS, and 100 μg/ml denatured salmon sperm DNA, at 65°C, followed by a washing treatment in a buffer solution containing 0.1×SSC and 0.1% SDS at 65°C (Condition 2). The latter (Condition 2) is more preferred. As for the factors to influence the stringency of hybridization, there are various kinds of factors other than the temperature condition mentioned above. It is possible for those skilled in the art to combine various kinds of such factors to achieve equivalent stringency to the stringency of hybridization exemplified above.

[0035] Moreover, the probe for detecting an arteriosclerosis marker gene of the present invention can be exemplified by a probe which comprises all or a part of antisense DNA for the gene having a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing. That is, it is a probe which comprises DNA having a nucleotide sequence complementary to the nucleotide sequence set forth in any one of SEQ ID NOs mentioned above, or a partial nucleotide sequence thereof.

These probes for detecting an arteriosclerosis marker gene may be appropriately labeled with a fluorescent label or the like.

[0036] Moreover, the DNA microarray or the DNA chip for detecting an arteriosclerosis marker gene of the present invention is used for the detection of the expression of the gene serving as the gene marker for diagnosing arteriosclerosis mentioned above, and for the diagnosis of an arteriosclerotic lesion through the detection, wherein the above-mentioned probe for detecting an arteriosclerosis marker gene is immobilized on a base plate. Regarding the above-mentioned probe for detecting an arteriosclerosis marker gene to be immobilized, it is either possible to use a single kind or a plurality of kinds thereof.

[0037] The DNA microarray or the DNA chip can be produced by a usual method. The DNA microarray can be obtained by, for example, spotting a solution containing respective probe(s) for detecting an arteriosclerosis marker gene that has been prepared in advance on a base plate and drying this plate. In addition, the DNA chip can be obtained by, for example, synthesizing DNA having a desired nucleotide sequence on a base plate by photolithography.

[0038] Hereunder is a description of the method for detecting arteriosclerosis of the present invention.

The method for detecting arteriosclerosis of the present invention is a method in which the above-mentioned polypeptide marker for diagnosing arteriosclerosis is used to detect the expression of an antibody (arteriosclerosis marker antibody) that is specifically bindable to the polypeptide marker for diagnosing arteriosclerosis, in a specimen blood (hereunder, referred to as the "detection method (1)"). In the specimen blood collected from a diseased patient with an arteriosclerotic lesion, the above-mentioned arteriosclerosis marker antibody is induced by the expression of the polypeptide serving as the polypeptide marker for diagnosing arteriosclerosis. So, it is possible to detect arteriosclerosis through detection of the arteriosclerosis marker antibody with use of the polypeptide marker for diagnosing arteriosclerosis.

[0039] The detection method (1) can be specifically exemplified by a method in which: the solid-phased polypeptide marker for diagnosing arteriosclerosis is contacted with a serum collected from a test subject so that the marker can bind to antibodies in the serum; unbound proteins are removed; next a labeled antibody (secondary antibody) that is specifically bindable to the antibodies in the serum is added to allow a reaction therebetween; and the signal from the labeled antibody is detected. As to the labeling substance for the abovementioned labeled antibody, it is possible to use an enzyme, a radioisotope, a fluorescent dye, biotin, digoxigenin, or the like, which has been enumerated as a substance to label the antibody of the present invention.

When an enzyme is used as a labeling substance, the amount of the antibody can be calculated by: adding a substrate which is decomposed to take a color by an enzymatic action; optically measuring the amount of the decomposed substrate to thereby obtain the enzymatic activity; converting this value into the amount of the antibody bound; and making a comparison between the converted value and a reference value. Alternatively, the amount of the antibody can also be obtained with high sensitivity by: adding a substrate which emits light by an enzymatic action; and measuring with a weak luminescence analyzer (luminometer).

When a radioisotope is used as a labeling substance, the amount of the antibody can be calculated by measuring the level of radiation emitted from the radioisotope with a scintillation counter or such a device. When a fluorescent dye is used as a labeling substance, the amount of the antibody can be calculated by measuring the quantity of fluorescence with a measurement device equipped with a fluorescence spectrometer or such a device.

[0040] In the detection method (1), the western blotting method can be applied. Moreover, it is also possible to isolate

a conjugate of the polypeptide marker for diagnosing arteriosclerosis, the antibody of the specimen blood, and the labeled antibody, by a known isolation method (a chromatography method, a salting-out method, an alcohol precipitation method, an enzyme method, an in-phase method, or the like), followed by the detection of the signal from the labeled antibody.

[0041] Moreover, in the diagnosis of arteriosclerosis by using the detection method (1), it is also possible to examine whether or not the arteriosclerosis marker antibody(antibodies) is(are) present in the specimen blood collected from a test subject so as to determine that the test subject showing the presence of one or more types of arteriosclerosis marker antibodies is a diseased patient with an arteriosclerotic lesion, or a person with a high risk of an arteriosclerotic lesion.

[0042] In addition, the method for detecting arteriosclerosis of the present invention is a method in which the above-mentioned probe for detecting an arteriosclerosis marker gene is used to detect the expression of a gene (arteriosclerosis marker gene) that is hybridizable with the probe for detecting an arteriosclerosis marker gene, in a specimen cell (hereunder, referred to as the "detection method (2)"). In the specimen cell collected from a diseased patient with an arteriosclerotic lesion, the arteriosclerosis marker gene is expressed. So, it is possible to detect arteriosclerosis through detection of the expression of the arteriosclerosis marker gene with use of the probe for detecting an arteriosclerosis marker gene.

[0043] The detection method (2) can be specifically exemplified by a method in which: a probe for detecting an arteriosclerosis marker gene, which has a nucleotide sequence as mentioned above in a suitable length for hybridization is prepared; a fluorescence label or such a label is appropriately added thereto; this labeled probe is contacted with a sample collected from a specimen cell to perform a hybridization reaction; and the expression of the gene serving as the gene marker for diagnosing arteriosclerosis is detected.

[0044] In the detection method (2), it is possible to employ a known detection method except for using the probe for detecting an arteriosclerosis marker gene of the present invention. For example, a northern blotting method can be employed. Moreover, in the detection method (2), any one of the above-mentioned probes for detecting an arteriosclerosis marker gene can be used. It is either possible to use a single kind of probe for detecting an arteriosclerosis marker gene or a plurality of kinds of probes for detecting an arteriosclerosis marker gene.

In addition, the detection method (2) may also use a DNA microarray or a DNA chip in which the probe(s) for detecting an arteriosclerosis marker gene is/are immobilized on a base plate.

[0045] Furthermore, in the detection method (2), it is also possible to employ quantitative or semi-quantitative PCR (Polymerase Chain Reaction) in order to amplify the arteriosclerosis marker gene in the sample collected from the specimen cell. The PCR may be either RT-PCR (reverse transcription PCR) or real-time RT-PCR. For carrying out the PCR, a primer set including a sense primer and an antisense primer for amplifying the arteriosclerosis marker gene is used. These primers can be appropriately constructed based on a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing.

On the completion of the amplification of the arteriosclerosis marker gene by such quantitative or semi-quantitative PCR in this way, the expression of the arteriosclerosis marker gene can be detected by using this sample. By so doing, the detection sensitivity can be improved.

[0046] Moreover, in the diagnosis of arteriosclerosis by using the detection method (2), it is possible to detect the arteriosclerosis marker gene in a test subject and compare the result with a result of a healthy subject detected by the same method to thereby determine that the test subject showing a large detection level is a diseased patient with an arteriosclerotic lesion, or a person with a high risk of an arteriosclerotic lesion.

[0047] In addition, the method for detecting arteriosclerosis of the present invention is a method in which the antibody bindable to, as an antigen, a polypeptide serving as the polypeptide marker for diagnosing arteriosclerosis of present invention, is used to detect the expression of a polypeptide (arteriosclerosis marker polypeptide) that is specifically bindable to the antibody, in a specimen sample (hereunder, referred to as the "detection method (3)"). In the specimen sample collected from a diseased patient with an arteriosclerotic lesion, the arteriosclerosis marker polypeptide is expressed. So, it is possible to detect arteriosclerosis through detection of the arteriosclerosis marker polypeptide with use of the antibody of the present invention.

[0048] The detection method (3) can be executed by a known immunoassay method except for using the antibody of the present invention. The immunoassay method can be exemplified by the western blotting method, the ELISA (Enzyme-Linked Immunosorbent Assay) method, a radioimmunoassay method, or a fluorescence antibody technique.

The antibody for use in the detection method (3) may be either monoclonal or polyclonal.

[0049] When the fluorescence antibody technique is applied to the detection method (3), either a direct fluorescence antibody test or an indirect fluorescence antibody test may be used. The direct fluorescence antibody test is a method in which an antibody for use in the detection is labeled with fluorescence, and then the antibody is contacted to a sample cell as being the test sample to bind them to each other so that a cell expressing the arteriosclerosis marker polypeptide can be labeled. In addition, the indirect fluorescence antibody test is a method in which a non-labeled antibody of the present invention is contacted to a sample cell to bind them to each other, and then the antibody is further bound to a labeled secondary antibody (anti-immunoglobulin antibody) so that a cell expressing the arteriosclerosis marker polypeptide can be labeled.

[0050] Moreover, when detecting arteriosclerosis through detection of the expression of the arteriosclerosis marker polypeptide, it is also possible, rather than using the antibody of the present invention as mentioned above, to use TOF-MASS to directly detect the arteriosclerosis marker polypeptide, or to use a chip in which a protein that is interactive with the arteriosclerosis marker polypeptide is immobilized on a base plate.

[0051] Moreover, in the diagnosis of arteriosclerosis by using the detection method (3), it is possible to examine whether or not the arteriosclerosis marker polypeptide(s) is(are) present in the specimen sample collected from a test subject so as to determine that the test subject showing the presence of one or more types of arteriosclerosis marker polypeptides is a diseased patient with an arteriosclerotic lesion, or a person with a high risk of an arteriosclerotic lesion.

[0052] The probe for detecting an arteriosclerosis marker gene for use in the detection of an arteriosclerotic lesion of the present invention, the DNA microarray or the DNA chip for detecting an arteriosclerosis marker gene in which the probe for detecting an arteriosclerosis marker gene is immobilized, and the antibody for detecting the arteriosclerosis marker polypeptide of the present invention can be prepared as a product of a kit for diagnosing arteriosclerosis which comprises at least one of these items and with which arteriosclerosis can be detected and diagnosed as mentioned above. In addition, the polypeptide marker for diagnosing arteriosclerosis of the present invention can also be prepared as a product of a kit for diagnosing arteriosclerosis with which arteriosclerosis can be detected and diagnosed as mentioned above.

[0053] When the polypeptide marker for diagnosing arteriosclerosis, the gene marker for diagnosing arteriosclerosis, the antibody, and the probe for detecting an arteriosclerosis marker gene of the present invention described above are jointly used with those of the Patent Document 22, arteriosclerosis can be detected with much higher accuracy.

Examples

[0054] Hereunder is a detailed description of the present invention with reference to Examples. However, the present invention is not to be limited by the following description.

Production Example

(Preparation of samples)

[0055]

(1) The subjects were patients with carotid artery stenoses who had visited our hospital or cooperative institutes. The reference (control) healthy subjects were selected from outpatients so that both groups had matched gender and age (±5 years). When they were visiting as outpatients or hospitalized in the neurosurgery department; 1) their families were explained that this study was to be conducted for research purposes and that cooperation with the study was not compulsory, and informed consents were obtained from them; 2) questions about the family history, the past history, the life style such as drinking and smoking habits, and the work style were asked; 3) blood was collected and separated into serum and corpuscle components and cryopreserved; and furthermore, 4) the clinical seriousness, the therapeutic process, the findings of the blood examination and the like were recorded on the basis of the medical record of the doctor. The patient blood as the analyte was separated into serum and cryopreserved at -80°C until the study was started. The antibodies and the medical records were used after encryption and anonymization.

(2) Regarding the target of screening with serum, commercial λZAP II phage vectors (STRATAGENE) recombined with a human microvascular endothelium-derived cDNA library were used.

(Expression cloning method)

[0056]

(3) The screening by the expression cloning method was conducted with reference to the method of St John, T et. al. (Science, 231, 845-850, 1986).

1) The above-mentioned phage vector of (2) was infected into *E. coli* (XL1-Blue) and cultured on a NZY agar medium (ϕ15 cm dish).

2) After confirming the emergence of plaques, an IPTG-treated nitrocellulose membrane was placed on the medium, and the phage-derived protein was expressed and transferred to the nitrocellulose membrane.

3) The patient serum which had been diluted 2000-fold with 1% BSA/PBS and the nitrocellulose membrane were incubated overnight to cause a reaction between the expression proteins and the antibodies in the serum

(serum IgG).
4) After washing, the alkaline phosphatase-labeled goat anti-human IgG antibody as a secondary antibody was reacted with the nitrocellulose membrane.
5) Serum IgG-recognizing clones were identified by using NBT (nitroblue terazolium) and BCIP (5-bromo-4-chloro-3-indolyl-phosphate) as a coloring reagent.
6) The positive clones were subjected to secondary and tertiary screening (in ϕ10 cm dish) and false positive clones were removed.
7) The selected phage was converted to pBlueScript with the ExAssist helper phage system (Stratagene, La Jolla, CA).
8) The plasmid was purified with use of the Plasmid Miniprep kit (Sigma).
9) The nucleotide sequences of the obtained clones were determined by a sequencer, and were subjected to a homology search using published databases. By so doing, the genes were identified and these clones were used as candidate antigen proteins.

(ELISA method)

[0057]

(4) ELISA method as secondary screening

1) The pBluescript including the insert of the candidate antigen protein was recombined into a protein expression and purification vector pGEX-4T (Amersham Bioscience). From the obtained nucleotide sequence information, restriction enzymes suitable for the recombination from pBluescript to pGEX-4T were selected, and treatments were done with restriction enzymes such as BamH I, Sal I, Not I, EcoR I, Xho I, and SmaI.
2) After agarose gel electophoresis, the band of interest was cut out by using the purification kit GeneElute Minus EtBr Spin Columns (SIGMA), and the restriction enzyme digested insert and the pGEX-4T were recovered.
3) The insert and the pGEX-4T were ligated with the Ligation-Convenience Kit (Nippongene) to thereby produce a plasmid containing the insert.
4) When there was no restriction enzyme suitable for some clones, the inserts thereof were produced by PCR. Primers having a restriction enzyme recognition site were produced in advance, and RNA extracted from aneurysmal tissue was used as a template to conduct reverse transcription PCR. Thereby, cDNA was produced. Another PCR was conducted to obtain the total length of the insert. Thereafter, the same treatment was carried out using the restriction enzymes and the ligation kit.
5) The obtained recombinant pGEX-4T was used to transform *E. coli* competent cell BL21 (Nippongene) modified for eukaryotic protein expression.
6) This product was cultured in an ampicillin-containing LB medium, and the expression of the insert DNA-derived protein was induced with IPTG.
7) *E. coli* was recovered through centrifugal separation and ruptured by sonication to separate into a soluble fraction and an insoluble fraction.
8) If the target protein was in the insoluble fraction, this was solubilized by using urea.
9) The antigen protein was purified with the glutathione-Sepharose (Amersham Pharmacia).
10) The antigen protein was injected in a 96-well ELISA plate at a concentration of 10 μg/ml, stored at 4°C overnight, and solid-phased.
11) After washing with PBS and blocking with a PBS solution containing 10% fetal bovine serum, patient serum and control serum (serum of healthy subject) were diluted 2000-fold and reacted with the solid-phased protein.
12) After washing with PBS, HRP-labeled goat anti-human IgG antibody was added.
13) A color was developed by adding a substrate, and the absorption at OD 490 nm was measured using a plate reader.

(Western blotting method)

[0058]

(5) Secondary screening by western blotting method

1)*E. coli* (SOLR, JM109, BL21) transformed with the pBluescript or the pGEX-4T including the insert of the candidate antigen protein obtained from the above, was cultured with 2 ml of LB ampicillin (50 μg/ml) overnight.
2) This was transferred to 20 ml of LB ampicillin and cultured for one hour, and was then added with IPTG to

give a final concentration of 1 mM. The resultant sample with IPTG and a control sample (without the addition of IPTG) were cultured for another 3 hours.
3) The culture liquid was centrifuged, and *E. coli* was recovered therefrom.
This was dissolved with a SDS sample buffer for use as a sample of the western method.
4) This sample was electophoresed on a 10% polyacrylamide gel, and the protein was transferred to a nitrocellulose membrane using a blotting apparatus.
5) This was blocked with 1% skim milk and then was added with a 2000-fold diluted patient serum as a primary antibody, followed by overnight incubation.
6) After washing with PBST (20 mM Tris-HCl (pH 7.6), 50 mM NaCl, 0.1% Tween-20), 30,000-fold diluted HRP-labeled goat anti-human IgG antibody was added and allowed to react for 20 minutes.
7) After washing with PBST, a luminescent reagent Immobilon Western (MILLIPORE) was used to effect light emission.
8) The membrane was exposed to a film and developed.
9) The band which became detectable depending on the IPTG treatment was assumed to be of an antigen protein.

Verification of the gene marker for diagnosing arteriosclerosis by sequencing

[0059] The nucleotide sequences of the genes (gene markers for diagnosing arteriosclerosis) of the detected clones were determined by sequencing. The thus determined nucleotide sequences were cross-checked with nucleotide sequences in published gene databases. As a result, the genes of the obtained clones had consistent nucleotide sequences with those of the genes that encode the polypeptides for diagnosing arteriosclerosis mentioned above.

Example 1

Measurement of the antibody titer by ELISA method

[0060] Using the experimental protocol of the Production Example mentioned above, the antibody levels of the thirteen out of the eighteen types of the detected arteriosclerosis diagnostic marker candidates were measured by ELISA, and the presence of the serum antibodies was confirmed. The results of the measurement are shown in Table 2.

[0061]

[Table 2]

Clone name	Patient (P)			Healthy subject (N)	
	Average	Standard deviation	p value (two-Sided)	Average	Standard deviation
S19A3	0.386	0.00912	0.0000	0.272	0.0624
TS27A2	0.306	0.1246	0.0011	0.229	0.0909
S21B1	0.206	0.1271	0.0078	0.146	0.0779
S25E1	0.346	0.3338	0.0145	0.210	0.1515
TS12D2	0.318	0.1959	0.0227	0.242	0.1019
S36C3	0.050	0.0407	0.0281	0.035	0.0207
N48B1	0.211	0.1109	0.0472	0.165	0.1065
S28D1	0.493	0.2525	0.0642	0.400	0.2251
TS27H1	0.093	0.0827	0.0645	0.067	0.0393
PA105	0.256	0.1414	0.0000	0.1417	0.0891
PA202	0.289	0.1546	0.0097	0.2157	0.1054
PA213	0.440	0.2052	0.0002	0.2955	0.1368
PA234	0.150	0.1001	0.0131	0.1046	0.0705

Example 2

Verification of the expression of arteriosclerosis marker genes by western blotting method.

[0062] The five types of clones of the candidate gene markers identified by the expression cloning method, that is, those unused in Example 1, were verified for the expression of the arteriosclerosis marker gene in arteriosclerosis patients by the western blotting method. The detection results thereof are shown in FIG. 1 (positive signal in western blots is indicated by the arrow in the figure.). FIG. 1(a) shows the results of Clone Name: S16D2 (SEQ ID NO: 22 of the Sequence Listing), FIG. 1(b) shows the results of Clone Name: S27D3 (SEQ ID NO: 24 of the Sequence Listing), FIG. 1(c) shows the results of Clone Name: S36E1 (SEQ ID NO: 26 of the Sequence Listing), FIG. 1(d) shows the results of Clone Name: S39D6 (SEQ ID NO: 28 of the Sequence Listing), and FIG. 1(e) shows the results of Clone Name: TS27B2 (SEQ ID NO: 30 of the Sequence Listing).

[0063] As shown in Table 2, with the thirteen types of candidate gene markers for diagnosing arteriosclerosis obtained from the screening of this Example, the measurement by the ELISA method showed a difference between the antibody titer of patients and the antibody titer of healthy subject serums. Furthermore, with eleven types of candidate gene markers, a significant difference was found.

In addition, as shown in FIG. 1, with five types of candidate gene markers obtained from the screening of this Example, positive signals for the specific reaction were confirmed by the western blotting method.

INDUSTRIAL APPLICABILITY

[0064] According to the polypeptide markers for diagnosing arteriosclerosis, the gene markers for diagnosing arteriosclerosis, the antibodies, the probes for detecting the arteriosclerosis marker genes, the DNA microarray or the DNA chip for detecting the arteriosclerosis marker genes, the method for detecting arteriosclerosis, and the kit for diagnosing arteriosclerosis of the present invention, arteriosclerosis can be readily detected with high accuracy. These can be favorably used for the early stage diagnosis of arteriosclerosis.

Sequence Listing

[0065]

SEQUENCE LISTING

<110> Fujikura Kasei Co., LTD
National University Corporation Chiba University

<120> POLYPEPTIDE MARKER FOR DIAGNOSIS OF ARTERIOSCLEROSIS, METHOD FOR DETECTION OF ARTERIOSCLEROSIS BY USING THE MAKER OR THE LIKE, AND KIT FOR DIAGNOSIS OF ARTERIOSCLEROSIS

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<141> 2009-08-14

<150> JP 2008-209210
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Met Arg Glu Ile Val His Leu Gln Ala Gly Gln Cys Gly Asn Gln Ile
1               5                  10                  15

Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
            20                  25                  30

Thr Gly Thr Tyr His Gly Asp Ser Asp Leu Gln Leu Glu Arg Ile Asn
        35                  40                  45

Val Tyr Tyr Asn Glu Ala Thr Gly Gly Lys Tyr Val Pro Arg Ala Val
    50                  55                  60

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Pro
65                  70                  75                  80

Phe Gly Gln Ile Phe Arg Pro Asp Asn Phe Val Phe Gly Gln Ser Gly
                85                  90                  95

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
            100                 105                 110

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Ala Glu Ser Cys Asp
        115                 120                 125

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
    130                 135                 140

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Ile Arg Glu Glu Tyr Pro
145                 150                 155                 160

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
                165                 170                 175

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Val His Gln Leu
            180                 185                 190

Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
        195                 200                 205

Asp Ile Cys Phe Arg Thr Leu Lys Leu Thr Thr Pro Thr Tyr Gly Asp
    210                 215                 220

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Cys Leu
225                 230                 235                 240

Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
                245                 250                 255

Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
            260                 265                 270

Leu Thr Ser Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
        275                 280                 285

Leu Thr Gln Gln Met Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
    290                 295                 300

Pro Arg His Gly Arg Tyr Leu Thr Val Ala Ala Val Phe Arg Gly Arg
305                 310                 315                 320

Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Asn Val Gln Asn Lys
                325                 330                 335

Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Thr Ala
            340                 345                 350

Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ala Thr Phe Ile
        355                 360                 365
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Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
370 375 380

Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
385 390 395 400

Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
405 410 415

Asp Leu Val Ser Glu Tyr Gln Gln Tyr Gln Asp Ala Thr Ala Glu Glu
420 425 430

Glu Gly Glu Phe Glu Glu Glu Ala Glu Glu Glu Val Ala
435 440 445

<210> 4
<211> 1338
<212> DNA
<213> Homo sapiens

<400> 4

atgagggaaa tcgtgcactt gcaggccggg cagtgcggca accaaatcgg cgccaagttt 60

tgggaggtga tcagcgatga gcacggcatc gaccccacgg gcacctacca cggggacagc 120

gacctgcagc tggaacgcat caacgtgtac tacaatgagg ccaccggcgg caagtacgtg 180

ccccgcgccg tgctcgtgga tctggagccc ggcaccatgg actccgtgcg ctcggggccc 240

ttcgggcaga tcttccggcc ggacaacttc gttttcggtc agagtggtgc tgggaacaac 300

tgggccaagg ggcactacac agaaggcgcg gagctggtgg actcggtgct ggatgttgtg 360

agaaaggagg ctgagagctg tgactgcctg cagggtttcc agctgaccca ctccctgggt 420

gggggggactg ggtctgggat gggtaccctc ctcatcagca agatccggga ggagtaccca 480

gacaggatca tgaacacgtt tagtgtggtg ccttcgccca aagtgtcaga cacagtggtg 540

gagccctaca acgccaccct ctcagtccac cagctcgtag aaaacacaga cgagacctac 600

tgcattgata acgaagctct ctacgacatt tgcttcagaa ccctaaagct gaccacgccc 660

acctatggtg acctgaacca cctggtgtct gctaccatga gtggggtcac cacctgcctg 720

cgcttcccag gccagctcaa tgctgacctg cggaagctgg ctgtgaacat ggtcccgttt 780

ccccggctgc acttcttcat gcccggcttt gccccactga ccagccgggg cagccagcag 840

taccgggcgc tgaccgtgcc cgagctcacc cagcagatgt ttgatgccaa gaacatgatg 900

gctgcctgcg acccccgcca tggccgctac ctgacggttg ccgccgtgtt caggggccgc 960

atgtccatga aggaggtgga tgagcaaatg cttaatgtcc aaaacaaaaa cagcagctat 1020

tttgttgagt ggatccccaa caatgtgaaa acggctgtct gtgacatccc acctcggggg 1080

ctaaaaatgt ccgccacctt cattggcaac agcacggcca tccaggagct gttcaagcgc 1140

atctccgagc agttcacggc catgttccgg cgcaaggcct tcctgcactg gtacacgggc 1200

gagggcatgg acgagatgga gttcaccgag gccgagagca acatgaatga cctggtgtcc 1260

gagtaccagc agtaccagga tgccacagcc gaggaggagg gcgagttcga ggaggaggct 1320

gaggaggagg tggcctag 1338

<210> 5
<211> 648
<212> PRT
<213> Homo sapiens

<400> 5

Met Glu Val Lys Gly Lys Lys Gln Phe Thr Gly Lys Ser Thr Lys Thr
1 5 10 15

Ala Gln Glu Lys Asn Arg Phe His Lys Asn Ser Asp Ser Gly Ser Ser
20 25 30

Lys Thr Phe Pro Thr Arg Lys Val Ala Lys Glu Gly Gly Pro Lys Val
35 40 45

Thr Ser Arg Asn Phe Glu Lys Ser Ile Thr Lys Leu Gly Lys Lys Gly
50 55 60

Val Lys Gln Phe Lys Asn Lys Gln Gln Gly Asp Lys Ser Pro Lys Asn
65 70 75 80

Lys Phe Gln Pro Ala Asn Lys Phe Asn Lys Lys Arg Lys Phe Gln Pro
85 90 95

Asp Gly Arg Ser Asp Glu Ser Ala Ala Lys Lys Pro Lys Trp Asp Asp
100 105 110

Phe Lys Lys Lys Lys Lys Glu Leu Lys Gln Ser Arg Gln Leu Ser Asp
115 120 125

Lys Thr Asn Tyr Asp Ile Val Val Arg Ala Lys Gln Met Trp Glu Ile
130 135 140

Leu Arg Arg Lys Asp Cys Asp Lys Glu Lys Arg Val Lys Leu Met Ser
145 150 155 160

Asp Leu Gln Lys Leu Ile Gln Gly Lys Ile Lys Thr Ile Ala Phe Ala
165 170 175

His Asp Ser Thr Arg Val Ile Gln Cys Tyr Ile Gln Tyr Gly Asn Glu
180 185 190

Glu Gln Arg Lys Gln Ala Phe Glu Glu Leu Arg Asp Asp Leu Val Glu
195 200 205

Leu Ser Lys Ala Lys Tyr Ser Arg Asn Ile Val Lys Lys Phe Leu Met
210 215 220

Tyr Gly Ser Lys Pro Gln Ile Ala Glu Ile Ile Arg Ser Phe Lys Gly
225 230 235 240

His Val Arg Lys Met Leu Arg His Ala Glu Ala Ser Ala Ile Val Glu
245 250 255

Tyr Ala Tyr Asn Asp Lys Ala Ile Leu Glu Gln Arg Asn Met Leu Thr
260 265 270

Glu Glu Leu Tyr Gly Asn Thr Phe Gln Leu Tyr Lys Ser Ala Asp His
275 280 285

Arg Thr Leu Asp Lys Val Leu Glu Val Gln Pro Glu Lys Leu Glu Leu
290 295 300

Ile Met Asp Glu Met Lys Gln Ile Leu Thr Pro Met Ala Gln Lys Glu
305 310 315 320

Ala Val Ile Lys His Ser Leu Val His Lys Val Phe Leu Asp Phe Phe
325 330 335

Thr Tyr Ala Pro Pro Lys Leu Arg Ser Glu Met Ile Glu Ala Ile Arg
340 345 350

Glu Ala Val Val Tyr Leu Ala His Thr His Asp Gly Ala Arg Val Ala
355 360 365

Met His Cys Leu Trp His Gly Thr Pro Lys Asp Arg Lys Val Ile Val
370 375 380

Lys Thr Met Lys Thr Tyr Val Glu Lys Val Ala Asn Gly Gln Tyr Ser
385 390 395 400

His Leu Val Leu Leu Ala Ala Phe Asp Cys Ile Asp Asp Thr Lys Leu
405 410 415

Val Lys Gln Ile Ile Ile Ser Glu Ile Ile Ser Ser Leu Pro Ser Ile
420 425 430

Val Asn Asp Lys Tyr Gly Arg Lys Val Leu Leu Tyr Leu Leu Ser Pro
435 440 445

Arg Asp Pro Ala His Thr Val Arg Glu Ile Ile Glu Val Leu Gln Lys
450 455 460

Gly Asp Gly Asn Ala His Ser Lys Lys Asp Thr Glu Val Arg Arg Arg
465 470 475 480

Glu Leu Leu Glu Ser Ile Ser Pro Ala Leu Leu Ser Tyr Leu Gln Glu
485 490 495

His Ala Gln Glu Val Val Leu Asp Lys Ser Ala Cys Val Leu Val Ser
500 505 510

Asp Ile Leu Gly Ser Ala Thr Gly Asp Val Gln Pro Thr Met Asn Ala
515 520 525

Ile Ala Ser Leu Ala Ala Thr Gly Leu His Pro Gly Gly Lys Asp Gly
530 535 540

Glu Leu His Ile Ala Glu His Pro Ala Gly His Leu Val Leu Lys Trp
545 550 555 560

Leu Ile Glu Gln Asp Lys Lys Met Lys Glu Asn Gly Arg Glu Gly Cys
565 570 575

Phe Ala Lys Thr Leu Val Glu His Val Gly Met Lys Asn Leu Lys Ser
580 585 590

Trp Ala Ser Val Asn Arg Gly Ala Ile Ile Leu Ser Ser Leu Leu Gln
595 600 605

Ser Cys Asp Leu Glu Val Ala Asn Lys Val Lys Ala Ala Leu Lys Ser
610 615 620

Leu Ile Pro Thr Leu Glu Lys Thr Lys Ser Thr Ser Lys Gly Ile Glu
625 630 635 640

Ile Leu Leu Glu Lys Leu Ser Thr
645

<210> 6
<211> 1947
<212> DNA
<213> Homo sapiens

<400> 6

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aacagatttc ataaaaatag tgattctggt tcttcaaaga catttccaac aaggaaagtt 120
gctaaagaag gtggacctaa agtcacatct aggaactttg agaaaagtat cacaaaactt 180
gggaaaaagg gtgtaaagca gttcaagaat aagcagcaag gggacaaatc accaaagaac 240
aaattccagc cggcaaataa attcaacaag aagagaaaat tccagccaga tggtagaagc 300
gatgaatcag cagccaagaa gcccaaatgg gatgacttca aaaagaagaa gaaagaactg 360
aagcaaagca gacaactcag tgataaaacc aactatgaca ttgttgttcg ggcaaagcag 420
atgtgggaga ttttaagaag aaaagactgt gacaaagaaa aaagagtaaa gttaatgagt 480
gatttgcaga agttgattca agggaaaatt aaaactattg catttgcaca cgattcaact 540
cgtgtgatcc agtgttacat tcagtatggt aatgaagaac agagaaaaca ggcttttgaa 600
gaattgcgag atgatttggt tgagttaagt aaagccaaat attcgagaaa tattgttaag 660
aaatttctca tgtatggaag taaaccacag attgcagaga taatcagaag ttttaaaggc 720
cacgtgagga agatgctgcg gcatgcggaa gcatcagcca tcgtggagta cgcatacaat 780
gacaaagcca ttttggagca gaggaacatg ctgacggaag agctctatgg gaacacattt 840
cagctttaca agtcagcaga tcaccgaact ctggacaaag tgttagaggt acagccagaa 900
aaattagaac ttattatgga tgaaatgaaa cagattctaa ctccaatggc ccaaaaggaa 960
gctgtgatta agcactcatt ggtgcataaa gtattcttgg actttttttac ctatgcaccc 1020
cccaaactca gatcagaaat gattgaagcc atccgcgaag cggtggtcta cctggcacac 1080
acacacgatg gcgccagagt ggccatgcac tgcctgtggc atggcacgcc caaggacagg 1140
aaagtgattg tgaaaacaat gaagacttat gttgaaaagg tggctaatgg ccaatactcc 1200
catttggttt tactggcggc atttgattgt attgatgata ctaagcttgt gaagcagata 1260
atcatatcag aaattatcag ttcattgcct agcatagtaa atgacaaata tggaaggaag 1320
gtcctattgt acttactaag ccccagagat cctgcacata cagtacgaga aatcattgaa 1380
gttctgcaaa aaggagatgg aaatgcacac agtaagaaag atacagaggt ccgcagacgg 1440
gagctcctag aatccatttc tccagctttg ttaagctacc tgcaagaaca cgcccaagaa 1500
gtggtgctag ataagtctgc gtgtgtgttg gtgtctgaca ttctgggatc tgccactgga 1560
gacgttcagc ctaccatgaa tgccatcgcc agcttggcag caacaggact gcatcctggt 1620
ggcaaggacg gagagcttca cattgcagaa catcctgcag gacatctagt tctgaagtgg 1680
ttaatagagc aagataaaaa gatgaaagaa aatgggagag aaggttgttt tgcaaaaaca 1740
cttgtagagc atgttggtat gaagaacctg aagtcctggg ctagtgtaaa tcgaggtgcc 1800
attattcttt ctagcctcct ccagagttgt gacctggaag ttgcaaacaa agtcaaagct 1860
gcactgaaaa gcttgattcc tacattggaa aaaaccaaaa gcaccagcaa aggaatagaa 1920
attctacttg aaaaactgag cacatag 1947

<210> 7
<211> 512
<212> PRT
<213> Homo sapiens

<400> 7

Met Ala Ile Leu Ser Leu Arg Ala Pro Gly Pro Trp Gln Ala Met Gln
1 5 10 15

Val Trp Ala Asp Arg Thr Leu Leu Thr Pro His Thr Gly Val Thr Ser
20 25 30

Gln Val Leu Gly Val Ala Ala Ala Val Met Thr Pro Leu Pro Gly Gly
35 40 45

His Ala Ala Gly Arg Thr Arg Glu Ala Arg Trp Asp Ala Met Glu Tyr
50 55 60

Asp Glu Lys Leu Ala Arg Phe Arg Gln Ala His Leu Asn Pro Phe Asn
65 70 75 80

Lys Gln Ser Gly Pro Arg Gln His Glu Gln Gly Pro Gly Glu Glu Val
85 90 95

Pro Asp Val Thr Pro Glu Glu Ala Leu Pro Glu Leu Pro Pro Gly Glu
100 105 110

Pro Glu Phe Arg Cys Pro Glu Arg Val Met Asp Leu Gly Leu Ser Glu
115 120 125

Asp His Phe Ser Arg Pro Val Gly Leu Phe Leu Ala Ser Asp Val Gln
130 135 140

Gln Leu Arg Gln Ala Ile Glu Glu Cys Lys Gln Val Ile Leu Glu Leu
145 150 155 160

Pro Glu Gln Ser Glu Lys Gln Lys Asp Ala Val Val Arg Leu Ile His
165 170 175

Leu Arg Leu Lys Leu Gln Glu Leu Lys Asp Pro Asn Glu Asp Glu Pro
180 185 190

Asn Ile Arg Val Leu Leu Glu His Arg Phe Tyr Lys Glu Lys Ser Lys
195 200 205

Ser Val Lys Gln Thr Cys Asp Lys Cys Asn Thr Ile Ile Trp Gly Leu
210 215 220

Ile Gln Thr Trp Tyr Thr Cys Thr Gly Cys Tyr Tyr Arg Cys His Ser
225 230 235 240

Lys Cys Leu Asn Leu Ile Ser Lys Pro Cys Val Ser Ser Lys Val Ser
245 250 255

His Gln Ala Glu Tyr Glu Leu Asn Ile Cys Pro Glu Thr Gly Leu Asp
260 265 270

Ser Gln Asp Tyr Arg Cys Ala Glu Cys Arg Ala Pro Ile Ser Leu Arg
275 280 285

Gly Val Pro Ser Glu Ala Arg Gln Cys Asp Tyr Thr Gly Gln Tyr Tyr
290 295 300

Cys Ser His Cys His Trp Asn Asp Leu Ala Val Ile Pro Ala Arg Val
305 310 315 320

Val His Asn Trp Asp Phe Glu Pro Arg Lys Val Ser Arg Cys Ser Met
325 330 335

Arg Tyr Leu Ala Leu Met Val Ser Arg Pro Val Leu Arg Leu Arg Glu
340 345 350

Ile Asn Pro Leu Leu Phe Ser Tyr Val Glu Glu Leu Val Glu Ile Arg
355 360 365

Lys Leu Arg Gln Asp Ile Leu Leu Met Lys Pro Tyr Phe Ile Thr Cys
370 37 380

Arg Glu Ala Met Glu Ala Arg Leu Leu Leu Gln Leu Gln Asp Arg Gln
385 390 395 400

His Phe Val Glu Asn Asp Glu Met Tyr Ser Val Gln Asp Leu Leu Asp
405 410 415

Val His Ala Gly Arg Leu Gly Cys Ser Leu Thr Glu Ile His Thr Leu
420 425 430

Phe Ala Lys His Ile Lys Leu Asp Cys Glu Arg Cys Gln Ala Lys Gly
435 440 445

Phe Val Cys Glu Leu Cys Arg Glu Gly Asp Val Leu Phe Pro Phe Asp
450 455 460

Ser His Thr Ser Val Cys Ala Asp Cys Ser Ala Val Phe His Arg Asp
465 470 475 480

Cys Tyr Tyr Asp Asn Ser Thr Thr Cys Pro Lys Cys Ala Arg Leu Ser
485 490 495

Leu Arg Lys Gln Ser Leu Phe Gln Glu Pro Gly Pro Asp Val Glu Ala
500 505 510

<210> 8
<211> 1539
<212> DNA
<213> Homo sapiens

<400> 8

gaatggccat cctgtccctg cgagcccctg ggccctggca ggcgatgcag gtatgggcag 60

acaggacgct gttgactccg cacaccggcg tgacttctca ggttctcggg gtggcagctg 120

cagtgatgac accgcttcct ggtggtcacg ccgcgggcag gacgcgggag gccaggtggg 180

atgctatgga atatgatgag aagctggccc gtttccggca ggcccacctc aacccttca 240

acaagcagtc tgggccgaga cagcatgagc agggccctgg ggaggaggtc ccggacgtca 300

ctcctgaaga ggccctgcct gagctgcccc ctggggagcc ggaattccgc tgccctgaac 360

gcgtgatgga tctcggcctg tctgaggacc acttctcccg ccctgtgggt ctgttcctgg 420

cctctgacgt ccagcagctg cggcaggcga tcgaggagtg caagcaggtg attctggagc 480

tgcccgagca gtcggagaag cagaaggatg ccgtggtgcg actcatccac ctccggctga 540

agctccagga gctgaaggac cccaatgagg atgagccaaa catccgagtg ctccttgagc 600

accgctttta caaggagaag agcaagagcg tcaagcagac ctgtgacaag tgtaacacca 660

tcatctgggg gctcattcag acctggtaca cctgcacagg gtgttattac cgctgtcaca 720

gtaagtgctt gaacctcatc tccaagccct gtgtgagctc caaagtcagc caccaagctg 780

aatacgaact gaacatctgc cctgagacag ggctggacag ccaggattac cgctgtgccg 840

agtgccgggc gcccatctct ctgcggggtg tgcccagtga ggccaggcag tgcgactaca 900

ccggccagta ctactgcagc cactgccact ggaacgacct ggctgtgatc cctgcacgcg 960

ttgtacacaa ctgggacttt gagcctcgaa aggtttctcg ctgcagcatg cgctacctgg 1020

cgctgatggt gtctcggccc gtactcaggc tccgggagat caaccctctg ctgttcagct 1080

acgtggagga gctggtggag attcgcaagc tgcgccagga catcctgctc atgaagccgt 1140

acttcatcac ctgcagggag gccatggagg ctcgtctgct gctgcagctc caggatcggc 1200

agcattttgt ggagaacgac gagatgtact ctgtccagga cctcctggac gtgcatgccg 1260

gccgcctggg ctgctcgctc accgagatcc acacgctctt cgccaagcac atcaagctgg 1320

actgcgagcg gtgccaggcc aagggcttcg tgtgtgagct ctgcagagag ggcgacgtgc 1380

tgttcccgtt cgacagccac acgtctgtgt gcgccgactg ctccgcggtc ttccacaggg 1440

actgctacta cgacaactcc accacttgtc ccaagtgtgc ccggctcagc ctgaggaagc 1500

agtcgctctt ccaggagcca ggtcccgatg tggaggcct 1539

<210> 9
<211> 1614
<212> PRT
<213> Homo sapiens

<400> 9

Met Ser Thr Pro Asp Pro Pro Leu Gly Gly Thr Pro Arg Pro Gly Pro
1 5 10 15

Ser Pro Gly Pro Gly Pro Ser Pro Gly Ala Met Leu Gly Pro Ser Pro
20 25 30

Gly Pro Ser Pro Gly Ser Ala His Ser Met Met Gly Pro Ser Pro Gly
35 40 45

Pro Pro Ser Ala Gly His Pro Ile Pro Thr Gln Gly Pro Gly Gly Tyr
50 55 60

Pro Gln Asp Asn Met His Gln Met His Lys Pro Met Glu Ser Met His
65 70 75 80

Glu Lys Gly Met Ser Asp Asp Pro Arg Tyr Asn Gln Met Lys Gly Met
85 90 95

Gly Met Arg Ser Gly Gly His Ala Gly Met Gly Pro Pro Pro Ser Pro
100 105 110

Met Asp Gln His Ser Gln Gly Tyr Pro Ser Pro Leu Gly Gly Ser Glu
115 120 125

His Ala Ser Ser Pro Val Pro Ala Ser Gly Pro Ser Ser Gly Pro Gln
130 135 140

Met Ser Ser Gly Pro Gly Gly Ala Pro Leu Asp Gly Ala Asp Pro Gln
145 150 155 160

Ala Leu Gly Gln Gln Asn Arg Gly Pro Thr Pro Phe Asn Gln Asn Gln
165 170 175

Leu His Gln Leu Arg Ala Gln Ile Met Ala Tyr Lys Met Leu Ala Arg
180 185 190

Gly Gln Pro Leu Pro Asp His Leu Gln Met Ala Val Gln Gly Lys Arg
195 200 205

Pro Met Pro Gly Met Gln Gln Gln Met Pro Thr Leu Pro Pro Pro Ser
210 215 220

Val Ser Ala Thr Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro
225 230 235 240

Gly Pro Gly Pro Ala Pro Pro Asn Tyr Ser Arg Pro His Gly Met Gly
245 250 255

Gly Pro Asn Met Pro Pro Pro Gly Pro Ser Gly Val Pro Pro Gly Met
260 265 270

Pro Gly Gln Pro Pro Gly Gly Pro Pro Lys Pro Trp Pro Glu Gly Pro
275 280 285

Met Ala Asn Ala Ala Ala Pro Thr Ser Thr Pro Gln Lys Leu Ile Pro
290 295 300

Pro Gln Pro Thr Gly Arg Pro Ser Pro Ala Pro Pro Ala Val Pro Pro
305 310 315 320

Ala Ala Ser Pro Val Met Pro Pro Gln Thr Gln Ser Pro Gly Gln Pro
325 330 335

Ala Gln Pro Ala Pro Met Val Pro Leu His Gln Lys Gln Ser Arg Ile
340 345 350

Thr Pro Ile Gln Lys Pro Arg Gly Leu Asp Pro Val Glu Ile Leu Gln
355 360 365

Glu Arg Glu Tyr Arg Leu Gln Ala Arg Ile Ala His Arg Ile Gln Glu
370 375 380

Leu Glu Asn Leu Pro Gly Ser Leu Ala Gly Asp Leu Arg Thr Lys Ala
385 390 395 400

Thr Ile Glu Leu Lys Ala Leu Arg Leu Leu Asn Phe Gln Arg Gln Leu
405 410 415

Arg Gln Glu Val Val Val Cys Met Arg Arg Asp Thr Ala Leu Glu Thr
420 425 430

Ala Leu Asn Ala Lys Ala Tyr Lys Arg Ser Lys Arg Gln Ser Leu Arg
435 440 445

Glu Ala Arg Ile Thr Glu Lys Leu Glu Lys Gln Gln Lys Ile Glu Gln
450 455 460

Glu Arg Lys Arg Arg Gln Lys His Gln Glu Tyr Leu Asn Ser Ile Leu
465 470 475 480

Gln His Ala Lys Asp Phe Lys Glu Tyr His Arg Ser Val Thr Gly Lys
485 490 495

Ile Gln Lys Leu Thr Lys Ala Val Ala Thr Tyr His Ala Asn Thr Glu
500 505 510

Arg Glu Gln Lys Lys Glu Asn Glu Arg Ile Glu Lys Glu Arg Met Arg
515 520 525

Arg Leu Met Ala Glu Asp Glu Glu Gly Tyr Arg Lys Leu Ile Asp Gln
530 535 540

Lys Lys Asp Lys Arg Leu Ala Tyr Leu Leu Gln Gln Thr Asp Glu Tyr
545 550 555 560

Val Ala Asn Leu Thr Glu Leu Val Arg Gln His Lys Ala Ala Gln Val
565 570 575

Ala Lys Glu Lys Lys Lys Lys Lys Lys Lys Lys Ala Glu Asn Ala
580 585 590

Glu Gly Gln Thr Pro Ala Ile Gly Pro Asp Gly Glu Pro Leu Asp Glu
595 600 605

Thr Ser Gln Met Ser Asp Leu Pro Val Lys Val Ile His Val Glu Ser
610 615 620

Gly Lys Ile Leu Thr Gly Thr Asp Ala Pro Lys Ala Gly Gln Leu Glu
625 630 635 640

Ala Trp Leu Glu Met Asn Pro Gly Tyr Glu Val Ala Pro Arg Ser Asp
645 650 655

Ser Glu Glu Ser Gly Ser Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
660 665 670

Gln Pro Gln Ala Ala Gln Pro Pro Thr Leu Pro Val Glu Glu Lys Lys
675 680 685

Lys Ile Pro Asp Pro Asp Ser Asp Asp Val Ser Glu Val Asp Ala Arg
690 695 700

His Ile Ile Glu Asn Ala Lys Gln Asp Val Asp Asp Glu Tyr Gly Val
705 710 715 720

Ser Gln Ala Leu Ala Arg Gly Leu Gln Ser Tyr Tyr Ala Val Ala His
725 730 735

Ala Val Thr Glu Arg Val Asp Lys Gln Ser Ala Leu Met Val Asn Gly
740 745 750

Val Leu Lys Gln Tyr Gln Ile Lys Gly Leu Glu Trp Leu Val Ser Leu
755 760 765

Tyr Asn Asn Asn Leu Asn Gly Ile Leu Ala Asp Glu Met Gly Leu Gly
770 775 780

Lys Thr Ile Gln Thr Ile Ala Leu Ile Thr Tyr Leu Met Glu His Lys
785 790 795 800

Arg Ile Asn Gly Pro Phe Leu Ile Ile Val Pro Leu Ser Thr Leu Ser
805 810 815

Asn Trp Ala Tyr Glu Phe Asp Lys Trp Ala Pro Ser Val Val Lys Val
820 825 830

Ser Tyr Lys Gly Ser Pro Ala Ala Arg Arg Ala Phe Val Pro Gln Leu
835 840 845

Arg Ser Gly Lys Phe Asn Val Leu Leu Thr Thr Tyr Glu Tyr Ile Ile
850 855 860

Lys Asp Lys His Ile Leu Ala Lys Ile Arg Trp Lys Tyr Met Ile Val
865 870 875 880

Asp Glu Gly His Arg Met Lys Asn His His Cys Lys Leu Thr Gln Val
885 890 895

Leu Asn Thr His Tyr Val Ala Pro Arg Arg Leu Leu Leu Thr Gly Thr
900 905 910

Pro Leu Gln Asn Lys Leu Pro Glu Leu Trp Ala Leu Leu Asn Phe Leu
915 920 925

Leu Pro Thr Ile Phe Lys Ser Cys Ser Thr Phe Glu Gln Trp Phe Asn
930 935 940

Ala Pro Phe Ala Met Thr Gly Glu Lys Val Asp Leu Asn Glu Glu Glu
945 950 955 960

Thr Ile Leu Ile Ile Arg Arg Leu His Lys Val Leu Arg Pro Phe Leu
965 970 975

Leu Arg Arg Leu Lys Lys Glu Val Glu Ala Gln Leu Pro Glu Lys Val
980 985 990

Glu Tyr Val Ile Lys Cys Asp Met Ser Ala Leu Gln Arg Val Leu Tyr
995 1000 1005

Arg His Met Gln Ala Lys Gly Val Leu Leu Thr Asp Gly Ser Glu Lys
1010 1015 1020

Asp Lys Lys Gly Lys Gly Gly Thr Lys Thr Leu Met Asn Thr Ile Met
1025 1030 1035 1040

Gln Leu Arg Lys Ile Cys Asn His Pro Tyr Met Phe Gln His Ile Glu
1045 1050 1055

Glu Ser Phe Ser Glu His Leu Gly Phe Thr Gly Gly Ile Val Gln Gly
1060 1065 1070

Leu Asp Leu Tyr Arg Ala Ser Gly Lys Phe Glu Leu Leu Asp Arg Ile
1075 1080 1085

Leu Pro Lys Leu Arg Ala Thr Asn His Lys Val Leu Leu Phe Cys Gln
1090 1095 1100

Met Thr Ser Leu Met Thr Ile Met Glu Asp Tyr Phe Ala Tyr Arg Gly
1105 1110 1115 1120

Phe Lys Tyr Leu Arg Leu Asp Gly Thr Thr Lys Ala Glu Asp Arg Gly
1125 1130 1135

Met Leu Leu Lys Thr Phe Asn Glu Pro Gly Ser Glu Tyr Phe Ile Phe
1140 1145 1150

Leu Leu Ser Thr Arg Ala Gly Gly Leu Gly Leu Asn Leu Gln Ser Ala
1155 1160 1165

Asp Thr Val Ile Ile Phe Asp Ser Asp Trp Asn Pro His Gln Asp Leu
1170 1175 1180

Gln Ala Gln Asp Arg Ala His Arg Ile Gly Gln Gln Asn Glu Val Arg
1185 1190 1195 1200

Val Leu Arg Leu Cys Thr Val Asn Ser Val Glu Glu Lys Ile Leu Ala
1205 1210 1215

Ala Ala Lys Tyr Lys Leu Asn Val Asp Gln Lys Val Ile Gln Ala Gly
1220 1225 1230

Met Phe Asp Gln Lys Ser Ser Ser His Glu Arg Arg Ala Phe Leu Gln
1235 1240 1245

Ala Ile Leu Glu His Glu Glu Gln Asp Glu Glu Glu Asp Glu Val Pro
1250 1255 1260

Asp Asp Glu Thr Val Asn Gln Met Ile Ala Arg His Glu Glu Glu Phe
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Asp Leu Phe Met Arg Met Asp Leu Asp Arg Arg Arg Glu Glu Ala Arg
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Asn Pro Lys Arg Lys Pro Arg Leu Met Glu Glu Asp Glu Leu Pro Ser
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Trp Ile Ile Lys Asp Asp Ala Glu Val Glu Arg Leu Thr Cys Glu Glu
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Glu Glu Glu Lys Met Phe Gly Arg Gly Ser Arg His Arg Lys Glu Val
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Asp Tyr Ser Asp Ser Leu Thr Glu Lys Gln Trp Leu Lys Ala Ile Glu
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Glu Gly Thr Leu Glu Glu Ile Glu Glu Glu Val Arg Gln Lys Lys Ser
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Ser Arg Lys Arg Lys Arg Asp Ser Asp Ala Gly Ser Ser Thr Pro Thr
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Thr Ser Thr Arg Ser Arg Asp Lys Asp Asp Glu Ser Lys Lys Gln Lys
1395 1400 1405

Lys Arg Gly Arg Pro Pro Ala Glu Lys Leu Ser Pro Asn Pro Pro Asn
1410 1415 1420

Leu Thr Lys Lys Met Lys Lys Ile Val Asp Ala Val Ile Lys Tyr Lys
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Asp Ser Ser Ser Gly Arg Gln Leu Ser Glu Val Phe Ile Gln Leu Pro
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Ser Arg Lys Glu Leu Pro Glu Tyr Tyr Glu Leu Ile Arg Lys Pro Val
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Asp Phe Lys Lys Ile Lys Glu Arg Ile Arg Asn His Lys Tyr Arg Ser
1475 1480 1485

Leu Asn Asp Leu Glu Lys Asp Val Met Leu Leu Cys Gln Asn Ala Gln
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Thr Phe Asn Leu Glu Gly Ser Leu Ile Tyr Glu Asp Ser Ile Val Leu
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Gln Ser Val Phe Thr Ser Val Arg Gln Lys Ile Glu Lys Glu Asp Asp
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Ser Glu Gly Glu Glu Ser Glu Glu Glu Glu Glu Gly Glu Glu Glu Gly
1540 1545 1550

Ser Glu Ser Glu Ser Arg Ser Val Lys Val Lys Ile Lys Leu Gly Arg
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Lys Glu Lys Ala Gln Asp Arg Leu Lys Gly Gly Arg Arg Arg Pro Ser
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<212> DNA
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<400> 10

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<212> PRT
<213> Homo sapiens

<400> 11

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Gly Ala Ser Cys Ser Val Gly Ala Pro Gly Gly Val Ser Met Phe Arg
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Trp Leu Glu Val Leu Glu Lys Glu Phe Asp Lys Ala Phe Val Asp Val
35 40 45

Asp Leu Leu Leu Gly Glu Ile Asp Pro Asp Gln Ala Asp Ile Thr Tyr
50 55 60

Glu Gly Arg Gln Lys Met Thr Ser Leu Ser Ser Cys Phe Ala Gln Leu
65 70 75 80

Cys His Lys Ala Gln Ser Val Ser Gln Ile Asn His Lys Leu Glu Ala
85 90 95

Gln Leu Val Asp Leu Lys Ser Glu Leu Thr Glu Thr Gln Ala Glu Lys
100 105 110

Val Val Leu Glu Lys Glu Val His Asp Gln Leu Leu Gln Leu His Ser
115 120 125

Ile Gln Leu Gln Leu His Ala Lys Thr Gly Gln Ser Ala Asp Ser Gly
130 135 140

Thr Ile Lys Ala Lys Leu Glu Arg Glu Leu Glu Ala Asn Lys Lys Glu
145 150 155 160

Lys Met Lys Glu Ala Gln Leu Glu Ala Glu Val Lys Leu Leu Arg Lys
165 170 175

Glu Asn Glu Ala Leu Arg Arg His Ile Ala Val Leu Gln Ala Glu Val
180 185 190

Tyr Gly Ala Arg Leu Ala Ala Lys Tyr Leu Asp Lys Glu Leu Ala Gly
195 200 205

Arg Val Gln Gln Ile Gln Leu Leu Gly Arg Asp Met Lys Gly Pro Ala
210 215 220

His Asp Lys Leu Trp Asn Gln Leu Glu Ala Glu Ile His Leu His Arg
225 230 235 240

His Lys Thr Val Ile Arg Ala Cys Arg Gly Arg Asn Asp Leu Lys Arg
245 250 255

Pro Met Gln Ala Pro Pro Gly His Asp Gln Asp Ser Leu Lys Lys Ser
260 265 270

Gln Gly Val Gly Pro Ile Arg Lys Val Leu Leu Leu Lys Glu Asp His
275 280 285

Glu Gly Leu Gly Ile Ser Ile Thr Gly Gly Lys Glu His Gly Val Pro
290 295 300

Ile Leu Ile Ser Glu Ile His Pro Gly Gln Pro Ala Asp Arg Cys Gly
305 310 315 320

Gly Leu His Val Gly Asp Ala Ile Leu Ala Val Asn Gly Val Asn Leu
325 330 335

Arg Asp Thr Lys His Lys Glu Ala Val Thr Ile Leu Ser Gln Gln Arg
340 345 350

Gly Glu Ile Glu Phe Glu Val Val Tyr Val Ala Pro Glu Val Asp Ser
355 360 365

Asp Asp Glu Asn Val Glu Tyr Glu Asp Glu Ser Gly His Arg Tyr Arg
370 375 380

Leu Tyr Leu Asp Glu Leu Glu Gly Gly Gly Asn Pro Gly Ala Ser Cys
385 390 395 400

Lys Asp Thr Ser Gly Glu Ile Lys Val Leu Gln Gly Phe Asn Lys Lys
405 410 415

Ala Val Thr Asp Thr His Glu Asn Gly Asp Leu Gly Thr Ala Ser Glu
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Thr Pro Leu Asp Asp Gly Ala Ser Lys Leu Asp Asp Leu His Thr Leu
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Tyr His Lys Lys Ser Tyr
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<212> DNA
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<400> 12

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<210> 13
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<213> Homo sapiens

<400> 13

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Asp Gly His Pro Glu Tyr Leu Ile Arg Trp Ser Val Leu Lys Cys Gly
35 40 45

Glu Val Gly Lys Val Gly Val Glu Glu Gly Lys Ala Glu His Ile Leu
50 55 60

Met Trp Leu Ser Ala Pro Glu Val Tyr Ala Asn Cys Pro Gly Leu Leu
65 70 75 80

Gly Glu Arg Ala Leu Ser Lys Gly Leu Gln His Glu Pro Ala Gly Val
85 90 95

Ser Gly Ser Phe Pro Arg Asp Pro Gly Gly Leu Asp Glu Val Ala Met
100 105 110

Gly Glu Met Glu Ala Asp Val Gln Ala Leu Val Arg Arg Ala Ala Arg
115 120 125

Gln Leu Ala Glu Ser Gly Thr Pro Ser Leu Thr Ala Ala Val Leu His
130 135 140

Thr Ile His Val Leu Ser Ala Tyr Ala Ser Ile Gly Pro Leu Thr Gly
145 150 155 160

Val Phe Arg Glu Thr Gly Ala Leu Asp Leu Leu Met His Met Leu Cys
165 170 175

Asn Pro Glu Pro Gln Ile Arg Arg Ser Ala Gly Lys Met Leu Gln Ala
180 185 190

Leu Ala Ala His Asp Ala Gly Ser Arg Ala His Val Leu Leu Ser Leu
195 200 205

Ser Gln Gln Asp Gly Ile Glu Gln His Met Asp Phe Asp Ser Arg Tyr
210 215 220

Thr Leu Leu Glu Leu Phe Ala Glu Thr Thr Ser Ser Glu Glu His Cys
225 230 235 240

Met Ala Phe Glu Gly Ile His Leu Pro Gln Ile Pro Gly Lys Leu Leu
245 250 255

Phe Ser Leu Val Lys Arg Tyr Leu Cys Val Thr Ser Leu Leu Asp Gln
260 265 270

Leu Asn Ser Ser Pro Glu Leu Gly Ala Gly Asp Gln Ser Ser Pro Cys
275 280 285

Ala Thr Arg Glu Lys Ser Arg Gly Gln Arg Glu Leu Glu Phe Ser Met
290 295 300

Ala Val Gly Asn Leu Ile Ser Glu Leu Val Arg Ser Met Gly Trp Ala
305 310 315 320

Arg Asn Leu Ser Glu Gln Gly Met Ser Pro Pro Arg Pro Thr Arg Ser
325 330 335

Ile Phe Gln Pro Tyr Ile Ser Gly Pro Ser Leu Leu Leu Pro Thr Ile
340 345 350

Val Thr Thr Pro Arg Arg Gln Gly Trp Val Phe Arg Gln Arg Ser Glu
355 360 365

Phe Ser Ser Arg Ser Gly Tyr Gly Glu Tyr Val Gln Gln Thr Leu Gln
370 375 380

Pro Gly Met Arg Val Arg Met Leu Asp Asp Tyr Glu Glu Ile Ser Ala
385 390 395 400

Gly Asp Glu Gly Glu Phe Arg Gln Ser Asn Asn Gly Ile Pro Pro Val
405 410 415

Gln Val Phe Trp Gln Ser Thr Gly Arg Thr Tyr Trp Val His Trp His
420 425 430

Met Leu Glu Ile Leu Gly Pro Glu Glu Ala Thr Glu Asp Lys Ala Ser
435 440 445

Ala Ala Val Glu Lys Gly Ala Gly Ala Thr Val Leu Gly Thr Ala Phe
450 455 460

Pro Ser Trp Asp Trp Asn Pro Met Asp Gly Leu Tyr Pro Leu Pro Tyr
465 470 475 480

Leu Gln Pro Glu Pro Gln Lys Asn Glu Arg Val Gly Tyr Leu Thr Gln
485 490 495

Ala Glu Trp Trp Glu Leu Leu Phe Phe Ile Lys Lys Leu Asp Leu Cys
500 505 510

Glu Gln Gln Pro Ile Phe Gln Asn Leu Trp Lys Asn Leu Asp Glu Thr
515 520 525

Leu Gly Glu Lys Ala Leu Gly Glu Ile Ser Val Ser Val Glu Met Ala
530 535 540

Glu Ser Leu Leu Gln Val Leu Ser Ser Arg Phe Glu Gly Ser Thr Leu
545 550 555 560

Asn Asp Leu Leu Asn Ser Gln Ile Tyr Thr Lys Tyr Gly Leu Leu Ser
565 570 575

Asn Glu Pro Ser Ser Ser Ser Thr Ser Arg Asn His Ser Cys Thr Pro
580 585 590

Asp Pro Glu Glu Glu Ser Lys Ser Glu Ala Ser Phe Ser Glu Glu Glu
595 600 605

Thr Glu Ser Leu Lys Ala Lys Ala Glu Ala Pro Lys Thr Glu Ala Glu
610 615 620

Pro Thr Lys Thr Arg Thr Glu Thr Pro Met Ala Gln Ser Asp Ser Gln
625 630 635 640

Leu Phe Asn Gln Leu Leu Val Thr Glu Gly Met Thr Leu Pro Thr Glu
645 650 655

Met Lys Glu Ala Ala Ser Glu Met Ala Arg Ala Leu Arg Gly Pro Gly
660 665 670

Pro Arg Ser Ser Leu Asp Gln His Val Ala Ala Val Val Ala Thr Val
675 680 685

Gln Ile Ser Ser Leu Asp Thr Asn Leu Gln Leu Ser Gly Leu Ser Ala
690 695 700

Leu Ser Gln Ala Val Glu Glu Val Thr Glu Arg Asp His Pro Leu Val
705 710 715 720

Arg Pro Asp Arg Ser Leu Arg Glu Lys Leu Val Lys Met Leu Val Glu
725 730 735

Leu Leu Thr Asn Gln Val Gly Glu Lys Met Val Val Val Gln Ala Leu
740 745 750

Arg Leu Leu Tyr Leu Leu Met Thr Lys His Glu Trp Arg Pro Leu Phe
755 760 765

Ala Arg Glu Gly Gly Ile Tyr Ala Val Leu Val Cys Met Gln Glu Tyr
770 775 780

Lys Thr Ser Val Leu Val Gln Gln Ala Gly Leu Ala Ala Leu Lys Met
785 790 795 800

Leu Ala Val Ala Ser Ser Ser Glu Ile Pro Thr Phe Val Thr Gly Arg
805 810 815

Asp Ser Ile His Ser Leu Phe Asp Ala Gln Met Thr Arg Glu Ile Phe
820 825 830

Ala Ser Ile Asp Ser Ala Thr Arg Pro Gly Ser Glu Ser Leu Leu Leu
835 840 845

Thr Val Pro Ala Ala Val Ile Leu Met Leu Asn Thr Glu Gly Cys Ser
850 855 860

Ser Ala Ala Arg Asn Gly Leu Leu Leu Leu Asn Leu Leu Leu Cys Asn
865 870 875 880

His His Thr Leu Gly Asp Gln Ile Ile Thr Gln Glu Leu Arg Asp Thr
885 890 895

Leu Phe Arg His Ser Gly Ile Ala Pro Arg Thr Glu Pro Met Pro Thr
900 905 910

Thr Arg Thr Ile Leu Met Met Leu Leu Asn Arg Tyr Ser Glu Pro Pro
915 920 925

Gly Ser Pro Glu Arg Ala Ala Leu Glu Thr Pro Ile Ile Gln Gly Gln
930 935 940

Asp Gly Ser Pro Glu Leu Leu Ile Arg Ser Leu Val Gly Gly Pro Ser
945 950 955 960

Ala Glu Leu Leu Leu Asp Leu Glu Arg Val Leu Cys Arg Glu Gly Ser
965 970 975

Pro Gly Gly Ala Val Arg Pro Leu Leu Lys Arg Leu Gln Gln Glu Thr
980 985 990

Gln Pro Phe Leu Leu Leu Leu Arg Thr Leu Asp Ala Pro Gly Pro Asn
995 1000 1005

Lys Thr Leu Leu Leu Ser Val Leu Arg Val Ile Thr Arg Leu Leu Asp
1010 1015 1020

Phe Pro Glu Ala Met Val Leu Pro Trp His Glu Val Leu Glu Pro Cys
1025 1030 1035 1040

Leu Asn Cys Leu Ser Gly Pro Ser Ser Asp Ser Glu Ile Val Gln Glu
1045 1050 1055

Leu Thr Cys Phe Leu His Arg Leu Ala Ser Met His Lys Asp Tyr Ala
1060 1065 1070

Val Val Leu Cys Cys Leu Gly Ala Lys Glu Ile Leu Ser Lys Val Leu
1075 1080 1085

Asp Lys His Ser Ala Gln Leu Leu Leu Gly Cys Glu Leu Arg Asp Leu
1090 1095 1100

Val Thr Glu Cys Glu Lys Tyr Ala Gln Leu Tyr Ser Asn Leu Thr Ser
1105 1110 1115 1120

Ser Ile Leu Ala Gly Cys Ile Gln Met Val Leu Gly Gln Ile Glu Asp
1125 1130 1135

His Arg Arg Thr His Gln Pro Ile Asn Ile Pro Phe Phe Asp Val Phe
1140 1145 1150

Leu Arg His Leu Cys Gln Gly Ser Ser Val Glu Val Lys Glu Asp Lys
1155 1160 1165

Cys Trp Glu Lys Val Glu Val Ser Ser Asn Pro His Arg Ala Ser Lys
1170 1175 1180

Leu Thr Asp His Asn Pro Lys Thr Tyr Trp Glu Ser Asn Gly Ser Thr
1185 1190 1195 1200

Gly Ser His Tyr Ile Thr Leu His Met His Arg Gly Val Leu Val Arg
1205 1210 1215

Gln Leu Thr Leu Leu Val Ala Ser Glu Asp Ser Ser Tyr Met Pro Ala
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Arg Val Val Val Phe Gly Gly Asp Ser Thr Ser Cys Ile Gly Thr Glu
1235 1240 1245

Leu Asn Thr Val Asn Val Met Pro Ser Ala Ser Arg Val Ile Leu Leu
1250 1255 1260

Glu Asn Leu Asn Arg Phe Trp Pro Ile Ile Gln Ile Arg Ile Lys Arg
1265 1270 1275 1280

Cys Gln Gln Gly Gly Ile Asp Thr Arg Val Arg Gly Val Glu Val Leu
1285 1290 1295

Gly Pro Lys Pro Thr Phe Trp Pro Leu Phe Arg Glu Gln Leu Cys Arg
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Arg Thr Cys Leu Phe Tyr Thr Ile Arg Ala Gln Ala Trp Ser Arg Asp
1315 1320 1325

Ile Ala Glu Asp His Arg Arg Leu Leu Gln Leu Cys Pro Arg Leu Asn
1330 1335 1340

Arg Val Leu Arg His Glu Gln Asn Phe Ala Asp Arg Phe Leu Pro Asp
1345 1350 1355 1360

Asp Glu Ala Ala Gln Ala Leu Gly Lys Thr Cys Trp Glu Ala Leu Val
1365 1370 1375

Ser Pro Leu Val Gln Asn Ile Thr Ser Pro Asp Ala Glu Gly Val Ser
1380 1385 1390

Ala Leu Gly Trp Leu Leu Asp Gln Tyr Leu Glu Gln Arg Glu Thr Ser
1395 1400 1405

Arg Asn Pro Leu Ser Arg Ala Ala Ser Phe Ala Ser Arg Val Arg Arg
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Leu Cys His Leu Leu Val His Val Glu Pro Pro Pro Gly Pro Ser Pro
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Glu Pro Ser Thr Arg Pro Phe Ser Lys Asn Ser Lys Gly Arg Asp Arg
1445 1450 1455

Ser Pro Ala Pro Ser Pro Val Leu Pro Ser Ser Ser Leu Arg Asn Ile
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Thr Gln Cys Trp Leu Ser Val Val Gln Glu Gln Val Ser Arg Phe Leu
1475 1480 1485

Ala Ala Ala Trp Arg Ala Pro Asp Phe Val Pro Arg Tyr Cys Lys Leu
1490 1495 1500

Tyr Glu His Leu Gln Arg Ala Gly Ser Glu Leu Phe Gly Pro Arg Ala
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Ala Phe Met Leu Ala Leu Arg Ser Gly Phe Ser Gly Ala Leu Leu Gln
1525 1530 1535

Gln Ser Phe Leu Thr Ala Ala His Met Ser Glu Gln Phe Ala Arg Tyr
1540 1545 1550

Ile Asp Gln Gln Ile Gln Gly Gly Leu Ile Gly Gly Ala Pro Gly Val
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Gly Asp Lys Ala Ala Ser Pro Ser Glu Leu Thr Cys Pro Pro Gly Trp
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Glu Trp Glu Asp Asp Ala Trp Ser Tyr Asp Ile Asn Arg Ala Val Asp
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Glu Lys Gly Trp Glu Tyr Gly Ile Thr Ile Pro Pro Asp His Lys Pro
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Lys Ser Trp Val Ala Ala Glu Lys Met Tyr His Thr His Arg Arg Arg
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Asn Leu Leu Ala Leu Asp Lys Asp Ser Phe Ser Asp Pro Tyr Ala His
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Ile Cys Phe Leu His Arg Ser Lys Thr Thr Glu Ile Ile His Ser Thr
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Glu Leu Phe Asp Asn Asp Gln Val Gly Lys Asp Glu Phe Leu Gly Arg
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Phe Met Lys Val Phe Leu Pro Lys Glu Glu Leu Tyr Met Pro Pro Leu
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Val Ile Lys Val Ile Asp His Arg Gln Phe Gly Arg Lys Pro Val Val
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Tyr Ile Gln Lys Gly Tyr Ser Lys Leu Lys Ile Tyr Asn Cys Glu Leu
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Val Glu Thr Arg Thr Leu His Ser Thr Phe Gln Pro Asn Ile Ser Gln
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Gly Lys Leu Gln Met Trp Val Asp Val Phe Pro Lys Ser Leu Gly Pro
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Pro Gly Pro Pro Phe Asn Ile Thr Pro Arg Lys Ala Lys Lys Tyr Tyr
1765 1770 1775

Leu Arg Val Ile Ile Trp Asn Thr Lys Asp Val Ile Leu Asp Glu Lys
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Ser Ile Thr Gly Glu Glu Met Ser Asp Ile Tyr Val Lys Gly Trp Ile
1795 1800 1805

Pro Gly Asn Glu Glu Asn Lys Gln Lys Thr Asp Val His Tyr Arg Ser
1810 1815 1820

Leu Asp Gly Glu Gly Asn Phe Asn Trp Arg Phe Val Phe Pro Phe Asp
1825 1830 1835 1840

Tyr Leu Pro Ala Glu Gln Leu Cys Ile Val Ala Lys Lys Glu His Phe
1845 1850 1855

Trp Ser Ile Asp Gln Thr Glu Phe Arg Ile Pro Pro Arg Leu Ile Ile
1860 1865 1870

Gln Ile Trp Asp Asn Asp Lys Phe Ser Leu Asp Asp Tyr Leu Gly Phe
1875 1880 1885

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1890 1895 1900

Lys Cys Arg Leu Asp Met Ile Pro Asp Leu Lys Ala Met Asn Pro Leu
1905 1910 1915 1920

Lys Ala Lys Thr Ala Ser Leu Phe Glu Gln Lys Ser Met Lys Gly Trp
1925 1930 1935

Trp Pro Cys Tyr Ala Glu Lys Asp Gly Ala Arg Val Met Ala Gly Lys
1940 1945 1950

Val Glu Met Thr Leu Glu Ile Leu Asn Glu Lys Glu Ala Asp Glu Arg
1955 1960 1965

Pro Ala Gly Lys Gly Arg Asp Glu Pro Asn Met Asn Pro Lys Leu Asp
1970 1975 1980

Leu Pro Asn Arg Pro Glu Thr Ser Phe Leu Trp Phe Thr Asn Pro Cys
1985 1990 1995 2000

Lys Thr Met Lys Phe Ile Val Trp Arg Arg Phe Lys Trp Val Ile Ile
2005 2010 2015

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Val Ile Thr Leu Thr Asp Gly His Ser Ala Trp Thr Gly Thr Val Ser
35 40 45

Glu Ser Glu Ile Ser Gln Glu Ala Asp Asp Met Ala Met Glu Lys Gly
50 55 60

Lys Tyr Val Gly Glu Leu Arg Lys Ala Leu Leu Ser Gly Ala Gly Pro
65 70 75 80

Ala Asp Val Tyr Thr Phe Asn Phe Ser Lys Glu Ser Cys Tyr Phe Phe
85 90 95

Phe Glu Lys Asn Leu Lys Asp Val Ser Phe Arg Leu Gly Ser Phe Asn
100 105 110

Leu Glu Lys Val Glu Asn Pro Ala Glu Val Ile Arg Glu Leu Ile Cys
115 120 125

Tyr Cys Leu Asp Thr Ile Ala Glu Asn Gln Ala Lys Asn Glu His Leu
130 135 140

Gln Lys Glu Asn Glu Arg Leu Leu Arg Asp Trp Asn Asp Val Gln Gly
145 150 155 160

Arg Phe Glu Lys Cys Val Ser Ala Lys Glu Ala Leu Glu Thr Asp Leu
165 170 175

Tyr Lys Arg Phe Ile Leu Val Leu Asn Glu Lys Lys Thr Lys Ile Arg
180 185 190

Ser Leu His Asn Lys Leu Leu Asn Ala Ala Gln Glu Arg Glu Lys Asp
195 200 205

Ile Lys Gln Glu Gly Glu Thr Ala Ile Cys Ser Glu Met Thr Ala Asp
210 215 220

Arg Asp Pro Val Tyr Asp Glu Ser Thr Asp Glu Glu Ser Glu Asn Gln
225 230 235 240

Thr Asp Leu Ser Gly Leu Ala Ser Ala Ala Val Ser Lys Asp Asp Ser
245 250 255

Ile Ile Ser Ser Leu Asp Val Thr Asp Ile Ala Pro Ser Arg Lys Arg
260 265 270

Arg Gln Arg Met Gln Arg Asn Leu Gly Thr Glu Pro Lys Met Ala Pro
275 280 285

Gln Glu Asn Gln Leu Gln Glu Lys Glu Asn Ser Arg Pro Asp Ser Ser
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35 40 45

Val Ser Pro Thr Gln Asp Ile Arg Leu Trp Val Ser Val Glu Asp Ala
50 55 60

Gln Met His Thr Val Thr Ile Trp Leu Thr Val Arg Pro Asp Met Thr
65 70 75 80

Val Ala Ser Leu Lys Asp Met Val Phe Leu Asp Tyr Gly Phe Pro Pro
85 90 95

Val Leu Gln Gln Trp Val Ile Gly Gln Arg Leu Ala Arg Asp Gln Glu
100 105 110

Thr Leu His Ser His Gly Val Arg Gln Asn Gly Asp Ser Ala Tyr Leu
115 120 125

Tyr Leu Leu Ser Ala Arg Asn Thr Ser Leu Asn Pro Gln Glu Leu Gln
130 135 140

Arg Glu Arg Gln Leu Arg Met Leu Glu Asp Leu Gly Phe Lys Asp Leu
145 150 155 160

Thr Leu Gln Pro Arg Gly Pro Leu Glu Pro Gly Pro Pro Lys Pro Gly
165 170 175

Val Pro Gln Glu Pro Gly Arg Gly Gln Pro Asp Ala Val Pro Glu Pro
180 185 190

Pro Pro Val Gly Trp Gln Cys Pro Gly Cys Thr Phe Ile Asn Lys Pro
195 200 205

Thr Arg Pro Gly Cys Glu Met Cys Cys Arg Ala Arg Pro Glu Ala Tyr
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Gln Val Pro Ala Ser Tyr Gln Pro Asp Glu Glu Glu Arg Ala Arg Leu
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Ala Gly Glu Glu Glu Ala Leu Arg Gln Tyr Gln Gln Arg Lys Gln Gln
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Gln Gln Glu Gly Asn Tyr Leu Gln His Val Gln Leu Asp Gln Arg Ser
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Cys Arg Glu Cys Leu Gln Gly Thr Ile Arg Asn Ser Gln Glu Ala Glu
305 310 315 320

Val Ser Cys Pro Phe Ile Asp Asn Thr Tyr Ser Cys Ser Gly Lys Leu
325 330 335

Leu Glu Arg Glu Ile Lys Ala Leu Leu Thr Pro Glu Asp Tyr Gln Arg
340 345 350

Phe Leu Asp Leu Gly Ile Ser Ile Ala Glu Asn Arg Ser Ala Phe Ser
355 360 365

Tyr His Cys Lys Thr Pro Asp Cys Lys Gly Trp Cys Phe Phe Glu Asp
370 375 380

Asp Val Asn Glu Phe Thr Cys Pro Val Cys Phe His Val Asn Cys Leu
385 390 395 400

Leu Cys Lys Ala Ile His Glu Gln Met Asn Cys Lys Glu Tyr Gln Glu
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Asp Leu Ala Leu Arg Ala Gln Asn Asp Val Ala Ala Arg Gln Thr Thr
420 425 430

Glu Met Leu Lys Val Met Leu Gln Gln Gly Glu Ala Met Arg Cys Pro
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Gln Cys Gln Ile Val Val Gln Lys Lys Asp Gly Cys Asp Trp Ile Arg
450 455 460

Cys Thr Val Cys His Thr Glu Ile Cys Trp Val Thr Lys Gly Pro Arg
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Val Asn Gly Ile Pro Cys His Pro Ser Cys Gln Asn Cys His
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<400> 21

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Leu Ile Leu His Ala Lys Val Ala Gln Lys Ser Tyr Gly Asn Glu Lys
50 55 60

Arg Phe Phe Cys Pro Pro Pro Cys Val Tyr Leu Met Gly Ser Gly Trp
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Lys Lys Lys Lys Glu Gln Met Glu Arg Asp Gly Cys Ser Glu Gln Glu
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Ser Gln Pro Cys Ala Phe Ile Gly Ile Gly Asn Ser Asp Gln Glu Met
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Gln Gln Leu Asn Leu Glu Gly Lys Asn Tyr Cys Thr Ala Lys Thr Leu
115 120 125

Tyr Ile Ser Asp Ser Asp Lys Arg Lys His Phe Met Leu Ser Val Lys
130 135 140

Met Phe Tyr Gly Asn Ser Asp Asp Ile Gly Val Phe Leu Ser Lys Arg
145 150 155 160

Ile Lys Val Ile Ser Lys Pro Ser Lys Lys Lys Gln Ser Leu Lys Asn
165 170 175

Ala Asp Leu Cys Ile Ala Ser Gly Thr Lys Val Ala Leu Phe Asn Arg
180 185 190

Leu Arg Ser Gln Thr Val Ser Thr Arg Tyr Leu His Val Glu Gly Gly
195 200 205

Asn Phe His Ala Ser Ser Gln Gln Trp Gly Ala Phe Phe Ile His Leu
210 215 220

Leu Asp Asp Asp Glu Ser Glu Gly Glu Glu Phe Thr Val Arg Asp Gly
225 230 235 240

Tyr Ile His Tyr Gly Gln Thr Val Lys Leu Val Cys Ser Val Thr Gly
245 250 255

Met Ala Leu Pro Arg Leu Ile Ile Arg Lys Val Asp Lys Gln Thr Ala
260 265 270

Leu Leu Asp Ala Asp Asp Pro Val Ser Gln Leu His Lys Cys Ala Phe
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Tyr Leu Lys Asp Thr Glu Arg Met Tyr Leu Cys Leu Ser Gln Glu Arg
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Ile Ile Gln Phe Gln Ala Thr Pro Cys Pro Lys Glu Pro Asn Lys Glu

305 310 315 320

Met Ile Asn Asp Gly Ala Ser Trp Thr Ile Ile Ser Thr Asp Lys Ala
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Glu Tyr Thr Phe Tyr Glu Gly Met Gly Pro Val Leu Ala Pro Val Thr
340 345 350

Pro Val Pro Val Val Glu Ser Leu Gln Leu Asn Gly Gly Gly Asp Val
355 360 365

Ala Met Leu Glu Leu Thr Gly Gln Asn Phe Thr Pro Asn Leu Arg Val
370 375 380

Trp Phe Gly Asp Val Glu Ala Glu Thr Met Tyr Arg Cys Gly Glu Ser
385 390 395 400

Met Leu Cys Val Val Pro Asp Ile Ser Ala Phe Arg Glu Gly Trp Arg
405 410 415

Trp Val Arg Gln Pro Val Gln Val Pro Val Thr Leu Val Arg Asn Asp
420 425 430

Gly Ile Ile Tyr Ser Thr Ser Leu Thr Phe Thr Tyr Thr Pro Glu Pro
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Gly Pro Arg Pro His Cys Ser Ala Ala Gly Ala Ile Leu Arg Ala Asn
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Ser Ser Gln Val Pro Pro Asn Glu Ser Asn Thr Asn Ser Glu Gly Ser
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Thr Val Val Ser
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agaactattg cacagccaaa acattgtata tatctgactc agacaagcga aagcacttca 420

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<211> 1354
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<400> 23

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Asn Lys Asn Ile Asp Asn Phe Leu Ser Arg Tyr Lys Asp Thr Ile Asn
50 55 60

Lys Ile Arg Asp Leu Arg Met Lys Ala Glu Asp Tyr Glu Val Val Lys
65 70 75 80

Val Ile Gly Arg Gly Ala Phe Gly Glu Val Gln Leu Val Arg His Lys
85 90 95

Ser Thr Arg Lys Val Tyr Ala Met Lys Leu Leu Ser Lys Phe Glu Met
100 105 110

Ile Lys Arg Ser Asp Ser Ala Phe Phe Trp Glu Glu Arg Asp Ile Met
115 120 125

Ala Phe Ala Asn Ser Pro Trp Val Val Gln Leu Phe Tyr Ala Phe Gln
130 135 140

Asp Asp Arg Tyr Leu Tyr Met Val Met Glu Tyr Met Pro Gly Gly Asp
145 150 155 160

Leu Val Asn Leu Met Ser Asn Tyr Asp Val Pro Glu Lys Trp Ala Arg
165 170 175

Phe Tyr Thr Ala Glu Val Val Leu Ala Leu Asp Ala Ile His Ser Met
180 185 190

Gly Phe Ile His Arg Asp Val Lys Pro Asp Asn Met Leu Leu Asp Lys
195 200 205

Ser Gly His Leu Lys Leu Ala Asp Phe Gly Thr Cys Met Lys Met Asn
210 215 220

Lys Glu Gly Met Val Arg Cys Asp Thr Ala Val Gly Thr Pro Asp Tyr
225 230 235 240

Ile Ser Pro Glu Val Leu Lys Ser Gln Gly Gly Asp Gly Tyr Tyr Gly
245 250 255

Arg Glu Cys Asp Trp Trp Ser Val Gly Val Phe Leu Tyr Glu Met Leu
260 265 270

Val Gly Asp Thr Pro Phe Tyr Ala Asp Ser Leu Val Gly Thr Tyr Ser
275 280 285

Lys Ile Met Asn His Lys Asn Ser Leu Thr Phe Pro Asp Asp Asn Asp
290 295 300

Ile Ser Lys Glu Ala Lys Asn Leu Ile Cys Ala Phe Leu Thr Asp Arg
305 310 315 320

Glu Val Arg Leu Gly Arg Asn Gly Val Glu Glu Ile Lys Arg His Leu
325 330 335

Phe Phe Lys Asn Asp Gln Trp Ala Trp Glu Thr Leu Arg Asp Thr Val
340 345 350

Ala Pro Val Val Pro Asp Leu Ser Ser Asp Ile Asp Thr Ser Asn Phe
355 360 365

Asp Asp Leu Glu Glu Asp Lys Gly Glu Glu Glu Thr Phe Pro Ile Pro
370 375 380

Lys Ala Phe Val Gly Asn Gln Leu Pro Phe Val Gly Phe Thr Tyr Tyr
385 390 395 400

Ser Asn Arg Arg Tyr Leu Ser Ser Ala Asn Pro Asn Asp Asn Arg Thr
405 410 415

Ser Ser Asn Ala Asp Lys Ser Leu Gln Glu Ser Leu Gln Lys Thr Ile
420 425 430

Tyr Lys Leu Glu Glu Gln Leu His Asn Glu Met Gln Leu Lys Asp Glu
435 440 445

Met Glu Gln Lys Cys Arg Thr Ser Asn Ile Lys Leu Asp Lys Ile Met
450 455 460

Lys Glu Leu Asp Glu Glu Gly Asn Gln Arg Arg Asn Leu Glu Ser Thr
465 470 475 480

Val Ser Gln Ile Glu Lys Glu Lys Met Leu Leu Gln His Arg Ile Asn
485 490 495

Glu Tyr Gln Arg Lys Ala Glu Gln Glu Asn Glu Lys Arg Arg Asn Val
500 505 510

Glu Asn Glu Val Ser Thr Leu Lys Asp Gln Leu Glu Asp Leu Lys Lys
515 520 525

Val Ser Gln Asn Ser Gln Leu Ala Asn Glu Lys Leu Ser Gln Leu Gln
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Lys Gln Leu Glu Glu Ala Asn Asp Leu Leu Arg Thr Glu Ser Asp Thr
545 550 555 560

Ala Val Arg Leu Arg Lys Ser His Thr Glu Met Ser Lys Ser Ile Ser
565 570 575

Gln Leu Glu Ser Leu Asn Arg Glu Leu Gln Glu Arg Asn Arg Ile Leu
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Glu Asn Ser Lys Ser Gln Thr Asp Lys Asp Tyr Tyr Gln Leu Gln Ala
595 600 605

Ile Leu Glu Ala Glu Arg Arg Asp Arg Gly His Asp Ser Glu Met Ile
610 615 620

Gly Asp Leu Gln Ala Arg Ile Thr Ser Leu Gln Glu Glu Val Lys His
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Leu Lys His Asn Leu Glu Lys Val Glu Gly Glu Arg Lys Glu Ala Gln
645 650 655

Asp Met Leu Asn His Ser Glu Lys Glu Lys Asn Asn Leu Glu Ile Asp
660 665 670

Leu Asn Tyr Lys Leu Lys Ser Leu Gln Gln Arg Leu Glu Gln Glu Val
675 680 685

Asn Glu His Lys Val Thr Lys Ala Arg Leu Thr Asp Lys His Gln Ser
690 695 700

Ile Glu Glu Ala Lys Ser Val Ala Met Cys Glu Met Glu Lys Lys Leu
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Lys Glu Glu Arg Glu Ala Arg Glu Lys Ala Glu Asn Arg Val Val Gln
725 730 735

Ile Glu Lys Gln Cys Ser Met Leu Asp Val Asp Leu Lys Gln Ser Gln
740 745 750

Gln Lys Leu Glu His Leu Thr Gly Asn Lys Glu Arg Met Glu Asp Glu
755 760 765

Val Lys Asn Leu Thr Leu Gln Leu Glu Gln Glu Ser Asn Lys Arg Leu
770 775 780

Leu Leu Gln Asn Glu Leu Lys Thr Gln Ala Phe Glu Ala Asp Asn Leu
785 790 795 800

Lys Gly Leu Glu Lys Gln Met Lys Gln Glu Ile Asn Thr Leu Leu Glu
805 810 815

Ala Lys Arg Leu Leu Glu Phe Glu Leu Ala Gln Leu Thr Lys Gln Tyr
820 825 830

Arg Gly Asn Glu Gly Gln Met Arg Glu Leu Gln Asp Gln Leu Glu Ala
835 840 845

Glu Gln Tyr Phe Ser Thr Leu Tyr Lys Thr Gln Val Lys Glu Leu Lys
850 855 860

Glu Glu Ile Glu Glu Lys Asn Arg Glu Asn Leu Lys Lys Ile Gln Glu
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Leu Gln Asn Glu Lys Glu Thr Leu Ala Thr Gln Leu Asp Leu Ala Glu
885 890 895

Thr Lys Ala Glu Ser Glu Gln Leu Ala Arg Gly Leu Leu Glu Glu Gln
900 905 910

Tyr Phe Glu Leu Thr Gln Glu Ser Lys Lys Ala Ala Ser Arg Asn Arg
915 920 925

Gln Glu Ile Thr Asp Lys Asp His Thr Val Ser Arg Leu Glu Glu Ala
930 935 940

Asn Ser Met Leu Thr Lys Asp Ile Glu Ile Leu Arg Arg Glu Asn Glu
945 950 955 960

Glu Leu Thr Glu Lys Met Lys Lys Ala Glu Glu Glu Tyr Lys Leu Glu
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Lys Glu Glu Glu Ile Ser Asn Leu Lys Ala Ala Phe Glu Lys Asn Ile
980 985 990

Asn Thr Glu Arg Thr Leu Lys Thr Gln Ala Val Asn Lys Leu Ala Glu
995 1000 1005

Ile Met Asn Arg Lys Asp Phe Lys Ile Asp Arg Lys Lys Ala Asn Thr
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Gln Asp Leu Arg Lys Lys Glu Lys Glu Asn Arg Lys Leu Gln Leu Glu
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Leu Asn Gln Glu Arg Glu Lys Phe Asn Gln Met Val Val Lys His Gln
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Lys Glu Leu Asn Asp Met Gln Ala Gln Leu Val Glu Glu Cys Ala His
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Arg Asn Glu Leu Gln Met Gln Leu Ala Ser Lys Glu Ser Asp Ile Glu
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Gln Leu Arg Ala Lys Leu Leu Asp Leu Ser Asp Ser Thr Ser Val Ala
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Ser Phe Pro Ser Ala Asp Glu Thr Asp Gly Asn Leu Pro Glu Ser Arg
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Ile Glu Gly Trp Leu Ser Val Pro Asn Arg Gly Asn Ile Lys Arg Tyr
1125 1130 1135

Gly Trp Lys Lys Gln Tyr Val Val Val Ser Ser Lys Lys Ile Leu Phe
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Tyr Asn Asp Glu Gln Asp Lys Glu Gln Ser Asn Pro Ser Met Val Leu
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Asp Ile Asp Lys Leu Phe His Val Arg Pro Val Thr Gln Gly Asp Val
1170 1175 1180

Tyr Arg Ala Glu Thr Glu Glu Ile Pro Lys Ile Phe Gln Ile Leu Tyr
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Ala Asn Glu Gly Glu Cys Arg Lys Asp Val Glu Met Glu Pro Val Gln
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Gln Ala Glu Lys Thr Asn Phe Gln Asn His Lys Gly His Glu Phe Ile
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Pro Thr Leu Tyr His Phe Pro Ala Asn Cys Asp Ala Cys Ala Lys Pro
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Leu Trp His Val Phe Lys Pro Pro Pro Ala Leu Glu Cys Arg Arg Cys
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His Val Lys Cys His Arg Asp His Leu Asp Lys Lys Glu Asp Leu Ile
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Cys Pro Cys Lys Val Ser Tyr Asp Val Thr Ser Ala Arg Asp Met Leu
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Leu Leu Ala Cys Ser Gln Asp Glu Gln Lys Lys Trp Val Thr His Leu
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Val Lys Lys Ile Pro Lys Asn Pro Pro Ser Gly Phe Val Arg Ala Ser
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<400> 24

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<400> 25

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Arg Trp Asn His Arg Tyr Asp Glu Trp Phe Cys Trp Asp Ser Pro Tyr
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Glu Asp Gly Ser Ser Glu Phe Gln Ile Asn Glu Gln Val Leu Ala Cys
85 90 95

Trp Ser Asp Cys Arg Phe Tyr Pro Ala Lys Val Thr Ala Val Asn Lys
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Asp Gly Thr Tyr Thr Val Lys Phe Tyr Asp Gly Val Val Gln Thr Val
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Lys His Ile His Val Lys Ala Phe Ser Lys Asp Gln Asn Ile Val Gly
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Asp Lys Arg Glu Lys Phe Lys Glu Gln Arg Lys Ala Thr Val Asn Val
165 170 175

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180 185 190

Gln Pro Asp Lys Glu Gly Lys Leu Ile Cys Ser Glu Lys Gly Lys Val
195 200 205

Ser Glu Lys Ser Leu Pro Lys Asn Glu Lys Glu Asp Lys Glu Asn Ile
210 215 220

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225 230 235 240

Pro Glu Asn Asp Ile Val Lys Ser Pro Gln Glu Asn Leu Arg Glu Pro
245 250 255

Lys Arg Lys Arg Gly Arg Pro Pro Ser Ile Ala Pro Thr Ala Val Asp
260 265 270

Ser Asn Ser Gln Thr Leu Gln Pro Ile Thr Leu Glu Leu Arg Arg Arg
275 280 285

Lys Ile Ser Lys Gly Cys Glu Val Pro Leu Lys Arg Pro Arg Leu Asp
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Lys Asn Ser Ser Gln Glu Lys Ser Lys Asn Tyr Ser Glu Asn Thr Asp
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Lys Asp Leu Ser Arg Arg Arg Ser Ser Arg Leu Ser Thr Asn Gly Thr
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His Glu Ile Leu Asp Pro Asp Leu Val Val Ser Asp Leu Val Asp Thr
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Asp Pro Leu Gln Asp Thr Leu Ser Ser Thr Lys Glu Ser Glu Glu Gly
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Gln Leu Lys Ser Ala Leu Glu Ala Gly Gln Val Ser Ser Ala Leu Thr
370 375 380

Cys His Ser Phe Gly Asp Gly Ser Gly Ala Ala Gly Leu Glu Leu Asn
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Cys Pro Ser Met Gly Glu Asn Thr Met Lys Thr Glu Pro Thr Ser Pro
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Leu Val Glu Leu Gln Glu Ile Ser Thr Val Glu Val Thr Asn Thr Phe
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Lys Lys Thr Asp Asp Phe Gly Ser Ser Asn Ala Pro Ala Val Asp Leu
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Asp His Lys Phe Arg Cys Lys Val Val Asp Cys Leu Lys Phe Phe Arg
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Lys Ala Lys Leu Leu His Tyr His Met Lys Tyr Phe His Gly Met Glu
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Lys Ser Leu Glu Pro Glu Glu Ser Pro Gly Lys Arg His Val Gln Thr
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Arg Gly Pro Ser Ala Ser Asp Lys Pro Ser Gln Glu Thr Leu Thr Arg
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Lys Arg Val Ser Ala Ser Ser Pro Thr Thr Lys Asp Lys Glu Lys Asn
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Lys Glu Lys Lys Phe Lys Glu Phe Val Arg Val Lys Pro Lys Lys Lys
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Ile Ser Asp Thr Ser Gln Glu Pro Ser Pro Pro Lys Ala Phe Ala Val
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Leu His Gly Pro Glu Ser Gly His His Lys Gly Lys Val Lys Ala Leu
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Asp Asp Glu Tyr Gly Gln Asp Val Asp Val Thr Thr Asn Pro Asp Glu
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Glu Leu Asp Gly Asp Asp Arg Tyr Asp Phe Glu Val Val Arg Cys Ile
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Cys Glu Val Gln Glu Glu Asn Asp Phe Met Ile Gln Cys Glu Glu Cys
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Gln Cys Trp Gln His Gly Val Cys Met Gly Leu Leu Glu Glu Asn Val
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Pro Glu Lys Tyr Thr Cys Tyr Val Cys Gln Asp Pro Pro Gly Gln Arg
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Pro Gly Phe Lys Tyr Trp Tyr Asp Lys Glu Trp Leu Ser Arg Gly His
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Met His Gly Leu Ala Phe Leu Glu Glu Asn Tyr Ser His Gln Asn Ala
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Lys Lys Ile Val Ala Thr His Gln Leu Leu Gly Asp Val Gln Arg Val
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Ile Glu Val Leu His Gly Leu Gln Leu Lys Met Ser Ile Leu Gln Ser
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Arg Glu His Pro Asp Leu Pro Leu Trp Cys Gln Pro Trp Lys Gln His
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Ser Gly Glu Gly Arg Ser His Phe Arg Asn Ile Pro Val Thr Asp Thr
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Glu Lys Pro Arg Pro Leu Ala Leu Pro Leu Pro Arg Ser Val Glu Glu
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Ser Tyr Ile Thr Ser Glu His Cys Tyr Gln Lys Pro Arg Ala Tyr Tyr
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Pro Ala Val Glu Gln Lys Leu Val Val Glu Thr Arg Gly Ser Ala Leu
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Pro Arg Leu Gly Trp Pro Leu Asp Gln Asp Arg Ser Lys Gly Asp Ser
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Asp Pro Lys Pro Gly Ser Pro Lys Val Lys Glu Tyr Val Ser Lys Lys
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His Val Glu Ser Leu Gln Asp Glu Val Thr His Arg MET Asp Ser Ile
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Glu Lys Glu Leu Asp Val Leu Glu Ser Trp Leu Asp Tyr Thr Gly Glu
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Leu Glu Pro Pro Glu Pro Leu Ala Arg Leu Pro Gln Leu Lys His Cys
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Ala Ser Leu Glu Lys Leu Val Asp Thr Ala Trp Leu Glu Ile Met Thr
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Lys Tyr Ala Val Gly Glu Glu Cys Asp Phe Glu Val Gly Lys Glu Lys
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Met Leu Lys Val Lys Ile Val Lys Ile His Pro Leu Glu Lys Val Asp
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Ser Asp Lys Glu Asn Ser Ser Gln Ile Ala Gln Asp His Gln Lys Lys
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Glu Thr Val Val Lys Glu Asp Glu Gly Arg Arg Glu Ser Ile Asn Asp
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Arg Ala Arg Arg Ser Pro Arg Lys Leu Pro Thr Ser Leu Lys Lys Gly
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Glu Arg Lys Trp Ala Pro Pro Lys Phe Leu Pro His Lys Tyr Asp Val
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Lys Leu Gln Asn Glu Asp Lys Ile Ile Ser Asn Val Pro Ala Asp Ser
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Leu Ile Arg Thr Glu Arg Pro Pro Asn Lys Glu Ile Val Arg Tyr Phe
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Ile Arg His Asn Ala Leu Arg Ala Gly Thr Gly Glu Asn Ala Pro Trp
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Val Val Glu Asp Glu Leu Val Lys Lys Tyr Ser Leu Pro Ser Lys Phe
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Ser Asp Phe Leu Leu Asp Pro Tyr Lys Tyr Met Thr Leu Asn Pro Ser
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Thr Lys Arg Lys Asn Thr Gly Ser Pro Asp Arg Lys Pro Ser Lys Lys
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Ser Lys Thr Asp Asn Ser Ser Leu Ser Ser Pro Leu Asn Pro Lys Leu
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Trp Cys His Val His Leu Lys Lys Ser Leu Ser Gly Ser Pro Leu Lys
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Val Lys Asn Ser Lys Asn Ser Lys Ser Pro Glu Glu His Leu Glu Glu
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Met Met Lys Met Met Ser Pro Asn Lys Leu His Thr Asn Phe His Ile
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Pro Lys Lys Gly Pro Pro Ala Lys Lys Pro Gly Lys His Ser Asp Lys
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Ser Thr Gly Asn Ser Lys Ser Pro Lys Lys Gly Leu Lys Thr Pro Lys
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Arg Leu Pro Glu Glu Leu Arg Ser Leu Val Gln Lys Arg Tyr Glu Leu
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Gln Lys Arg Tyr Glu Asp Gln Glu Leu Thr Gly Lys Asn Leu Pro Ala
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Phe Arg Leu Val Asp Thr Pro Glu Gly Leu Pro Asn Thr Leu Phe Gly
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Asp Val Ala Met Val Val Glu Phe Leu Ser Cys Tyr Ser Gly Leu Leu
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Leu Ser Ala Asp Lys Gly Gly Phe Leu Tyr Leu Asn Arg Val Leu Val
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Glu Leu Gly Met Lys Leu Ser Glu Ile Pro Leu Thr Leu His Ser Val
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Ser Glu Gly Ser Asp Thr Asp Asp Asn Lys Asp Ser Ala Ala Phe Glu
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Asp Asn Glu Val Gln Asp Glu Phe Leu Glu Lys Leu Glu Thr Ser Glu
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Phe Phe Glu Leu Thr Ser Glu Glu Lys Leu Gln Ile Leu Thr Ala Leu
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Cys His Arg Ile Leu Met Thr Tyr Ser Val Gln Asp His Met Glu Thr
755 760 765

Arg Gln Gln Met Ser Ala Glu Leu Trp Lys Glu Arg Leu Ala Val Leu
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Lys Glu Glu Asn Asp Lys Lys Arg Ala Glu Lys Gln Lys Arg Lys Glu
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Met Glu Ala Lys Asn Lys Glu Asn Gly Lys Val Glu Asn Gly Leu Gly
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Lys Thr Asp Arg Lys Lys Glu Ile Val Lys Phe Glu Pro Gln Val Asp
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Thr Glu Ala Glu Asp Met Ile Ser Ala Val Lys Ser Arg Arg Leu Leu
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Ala Ile Gln Ala Lys Lys Glu Arg Glu Ile Gln Glu Arg Glu Met Lys
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Val Lys Leu Glu Arg Gln Ala Glu Glu Glu Arg Ile Arg Lys His Lys
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Val Met Arg Arg Thr Pro Ile Gly Thr Asp Arg Asn His Asn Arg Tyr
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Trp Leu Phe Ser Asp Glu Val Pro Gly Leu Phe Ile Glu Lys Gly Trp
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Val His Asp Ser Ile Asp Tyr Arg Phe Asn His His Cys Lys Asp His
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Leu Cys Asp Ser Gln Lys Glu Leu Asp Glu Leu Leu Asn Cys Leu His
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Tyr Gln Asp Ile Ile His Ser Ile His Leu Ala Arg Lys Pro Asn Leu
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His Lys His Leu Pro Gly His Pro Tyr Val Arg Arg Lys Arg Lys Lys
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Claims

1. A polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 of the Sequence Listing, or a partial amino acid sequence thereof.

2. A gene marker for diagnosing arteriosclerosis, which comprises a gene represented by a nucleotide sequence that encodes the amino acid sequence according to claim 1, or a partial amino acid sequence thereof.

3. A gene marker for diagnosing arteriosclerosis, which comprises a gene having a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8,10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing, or a partial nucleotide sequence thereof.

4. An antibody specifically bindable to the polypeptide according to claim 1 as an antigen.

5. A probe for detecting an arteriosclerosis marker gene, which comprises all or a part of DNA that is hybridizable with the gene according to either one of claim 2 and claim 3 under a stringent condition.

6. The probe for detecting an arteriosclerosis marker gene according to claim 5, which comprises all or a part of antisense DNA for the gene according to claim 3.

7. A DNA microarray or a DNA chip for detecting an arteriosclerosis marker gene, wherein the probe for detecting an arteriosclerosis marker gene according to claim 5 and/or the probe for detecting an arteriosclerosis marker gene according to claim 6 is/are immobilized on a base plate.

8. A method for detecting arteriosclerosis, wherein the antibody according to claim 4 is used to detect the expression of an arteriosclerosis marker polypeptide that is specifically bindable to the antibody, in a specimen sample.

9. A method for detecting arteriosclerosis, wherein the polypeptide marker for diagnosing arteriosclerosis according to claim 1 is used to detect the expression of an arteriosclerosis marker antibody that is specifically bindable to the polypeptide marker for diagnosing arteriosclerosis, in specimen blood.

10. A method for detecting arteriosclerosis, wherein the probe for detecting an arteriosclerosis marker gene according to either one of claim 5 and claim 6 is used to detect the expression of an arteriosclerosis marker gene that is

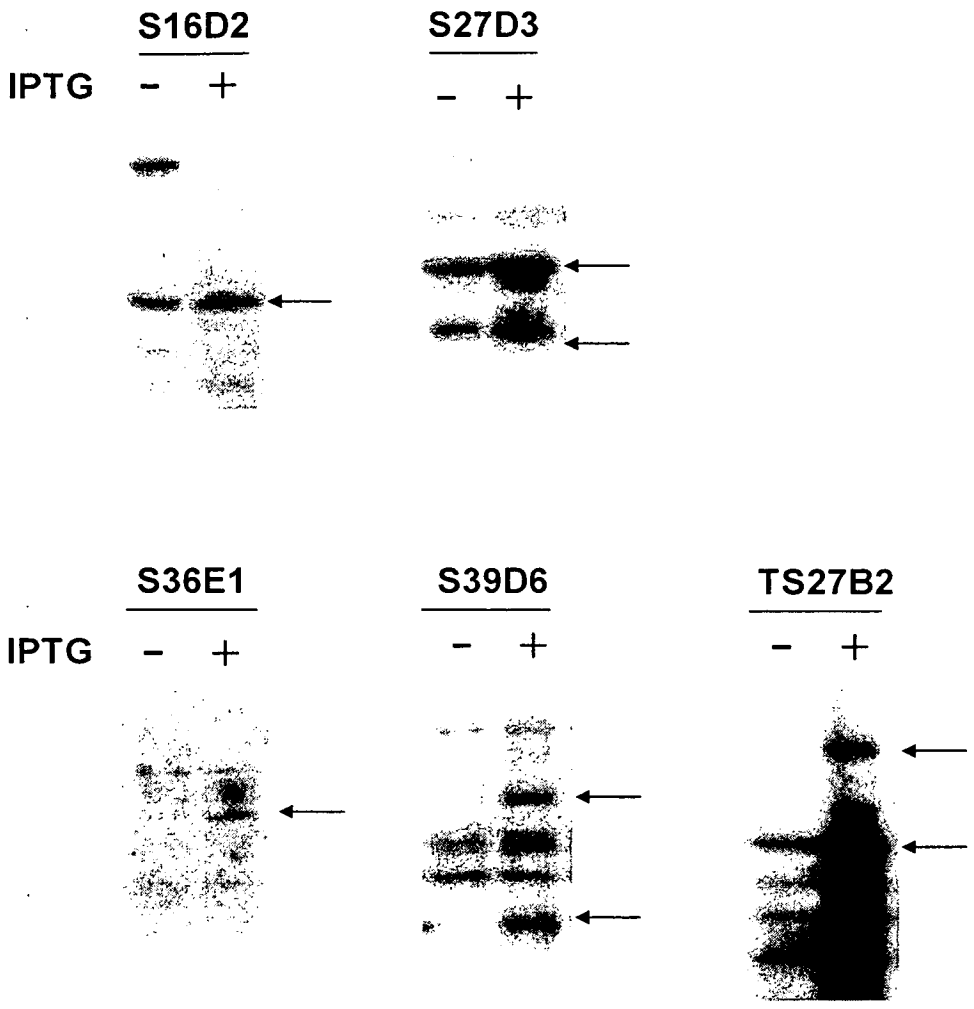
hybridizable with the probe for detecting an arteriosclerosis marker gene, in a specimen cell.

11. A method for detecting arteriosclerosis, wherein a primer is constructed based on a nucleotide sequence set forth in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36 of the Sequence Listing, and PCR is conducted with use of the primer to detect the expression of an arteriosclerosis marker gene.

12. A kit for diagnosing arteriosclerosis, including at least one item selected from the group consisting of the probe for detecting an arteriosclerosis marker gene according to either one of claim 5 and claim 6, the DNA microarray or the DNA chip for detecting an arteriosclerosis marker gene according to claim 7, and the antibody according to claim 4.

13. A kit for diagnosing arteriosclerosis, including a polypeptide marker for diagnosing arteriosclerosis which comprises a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 of the Sequence Listing, or a partial amino acid sequence thereof.

FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/064363

A. CLASSIFICATION OF SUBJECT MATTER
C12N15/09(2006.01)i, *C07K14/47*(2006.01)i, *C07K16/18*(2006.01)i, *C12Q1/68*(2006.01)i, *G01N33/53*(2006.01)i, *G01N37/00*(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N15/09, C07K14/47, C07K16/18, C12Q1/68, G01N33/53, G01N37/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2009
Kokai Jitsuyo Shinan Koho 1971-2009 Toroku Jitsuyo Shinan Koho 1994-2009

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA/BIOSIS/MEDLINE/WPIDS(STN), JSTPlus/JMEDPlus/JST7580(JDreamII), GenBank/EMBL/DDBJ/GeneSeq, SwissProt/PIR/GeneSeq

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2005-168498 A (Japan Science and Technology Agency), 30 June 2005 (30.06.2005), (Family: none)	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 November, 2009 (04.11.09)	17 November, 2009 (17.11.09)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/064363

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
See extra sheet.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2009/064363

Continuation of Box No.III of continuation of first sheet(2)

"JP 2005-168498 A (Japan Science and Technology Agency) 30 June 2005 (30.06.2005) (family: none)", which is cited as "Patent reference 22" in the description of the present application, describes a gene marker for diagnosing arteriosclerosis which is produced by searching for a protein capable of being expressed in the serum of a patient suffering from an arteriosclerotic lesion and a peptide marker encoded by the gene marker. Therefore, a fact that inventions share only a common matter "they relate a gene marker and a peptide marker for diagnosing arteriosclerosis" does not mean that the inventions have the same "special technical feature". Therefore, a pair of a polypeptide marker selected from 18 polypeptide markers recited in the claims and a gene marker selected from 18 gene markers recited in the claims and corresponding to the polypeptide marker cannot be regarded as a group of inventions so linked to each other as to form a single general inventive concept. Thus, the present application includes 18 inventions respectively corresponding to the 18 markers recited in the claims. Namely, claims 1-13 include the following groups of inventions.

(1) Inventions relating to "a polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having the amino acid sequence depicted in SEQ ID NO:1 shown in the Sequence Listing or a partial amino acid sequence thereof" and "a gene marker for diagnosing arteriosclerosis, which comprises a gene having the nucleotide sequence depicted in SEQ ID NO:2 shown in the Sequence Listing or a partial nucleotide sequence thereof" which corresponds to the polypeptide.

(2) Inventions relating to "a polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having the amino acid sequence depicted in SEQ ID NO:3 shown in the Sequence Listing or a partial amino acid sequence thereof" and "a gene marker for diagnosing arteriosclerosis, which comprises a gene having the nucleotide sequence depicted in SEQ ID NO:4 shown in the Sequence Listing or a partial nucleotide sequence thereof" which corresponds to the polypeptide.

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(18) Inventions relating to "a polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having the amino acid sequence depicted in SEQ ID NO:35 shown in the Sequence Listing or a partial amino acid sequence thereof" and "a gene marker for diagnosing arteriosclerosis, which comprises a gene having the nucleotide sequence depicted in SEQ ID NO:36 shown in the Sequence Listing or a partial nucleotide sequence thereof" which corresponds to the polypeptide.

Since the additional search fees were not paid by the applicant by the due date of the payment, this international search report was prepared on the first claimed invention, i.e., the parts of the inventions included within claims 1-13 which relate to item (1) above.

Form PCT/ISA/210 (extra sheet) (April 2007)

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	用于诊断动脉硬化的多肽标记物，使用该制造者等检测动脉硬化的方法，以及用于诊断动脉硬化的试剂盒		
公开(公告)号	EP2319924A4	公开(公告)日	2012-01-25
申请号	EP2009806761	申请日	2009-08-14
[标]申请(专利权)人(译)	藤仓化成株式会社		
申请(专利权)人(译)	FUJIKURA KASEI CO.，LTD. 国立大学法人千叶大学		
当前申请(专利权)人(译)	FUJIKURA KASEI CO.，LTD. 国立大学法人千叶大学		
[标]发明人	NAKAMURA RIKA KURODA HIDEYUKI TOMIYOSHI GO HIWASA TAKAKI TAKIGUCHI MASAKI SAEKI NAOKATSU MACHIDA TOSHIO		
发明人	NAKAMURA RIKA KURODA HIDEYUKI TOMIYOSHI GO HIWASA TAKAKI TAKIGUCHI MASAKI SAEKI NAOKATSU MACHIDA TOSHIO		
IPC分类号	C12N15/09 C07K14/47 C07K16/18 C12Q1/68 G01N33/53 G01N37/00 G01N33/68		
CPC分类号	C07K14/47 C12Q1/6883 C12Q2600/158 G01N33/6893 G01N2800/323 G01N33/5302		
代理机构(译)	WRIGHT，ANDREW JOHN		
优先权	2008209210 2008-08-15 JP		
其他公开文献	EP2319924A1 EP2319924B1		
外部链接	Espacenet		

摘要(译)

公开了用于诊断动脉硬化的多肽标记物;用于诊断动脉硬化的基因标记物;抗体;用于检测动脉硬化标志物基因的探针;用于检测动脉硬化标记基因的DNA微阵列或DNA芯片;一种检测动脉硬化的方法;和用于诊断动脉硬化的试剂盒;可以检测到动脉硬化病变，并且准确性大大提高。具体公开了：用于诊断动脉硬化的多肽标记物，其包含具有SEQ ID NO：1,3,5,7,9,11,13,15,17,19中任一个所示氨基酸序列的多肽，序列表中的21,23,25,27,29,31,33和35，或其部分氨基酸序列;编码氨基酸序列的基因;用于检测基因的探针; DNA微阵列或包含该探针的DNA芯片;可与多肽结合的抗体作为抗原;包括上述任何一项的试剂盒;以及通过使用上述任一项检测动脉硬化的方法。

(continued)

	Clone Name	SEQ ID NO.	Accession No.	Gene Name
2	TS27A2	4	NM_006088	tubulin, beta 2C (TUBB2C)
3	S21B1	6	NM_014878	KIAA0020 (KIAA0020)
4	S25E1	8	NM_207514	differentially expressed in FDCP 8 homolog (mouse) (DEF8)
5	TS12D2	10	NM_001128847	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4)
6	S36C3	12	NM_001017408	golgi associated PDZ and coiled-coil motif containing (GOPC)
7	N48B1	14	NM_015089	p53-associated parkin-like cytoplasmic protein (PARC)
8	S28D1	16	NM_133337	fer-1-like 3, myoferlin (C. elegans) (FER1 L3)
9	TS27H1	18	NM_022406	X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4)
10	PA105	20	NM_001229	RanBP-type and C3HC4-type zinc finger containing 1 (RBCK1)
11	S16D2	22	NM_005349	recombinations signal binding protein for immunoglobulin kappa J region (RBPJ)
12	S27D3	24	NM_005406	Rho-associated, coiled-coil containing protein kinase 1 (ROCK1)
13	S36E1	26	NM_016436	PHD finger protein 20 (PHF20)
14	S39D6	28	NM_ 032408	bromodomain adjacent to zinc finger domain, 1B (BAZ1B)
15	TS27B2	30	NM_014377	zuotin related factor 1 (ZRF1)
16	PA202	32	NM_003692	transmembrane protein with EGF-like and two follistatin-like domains 1 (TMEFF1)
17	PA213	34	NM_006807	chromobox homolog 1 (HP1 beta homolog Drosophila) (CBX1)
18	PA234	36	BC030642	PARK2 co-regulated (PACRG)