



(11) **EP 2 319 924 A1**

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 153(4) EPC

(43) Date of publication:
11.05.2011 Bulletin 2011/19

(21) Application number: **09806761.4**

(22) Date of filing: **14.08.2009**

(51) Int Cl.:
C12N 15/09 (2006.01) **C07K 14/47** (2006.01)
C07K 16/18 (2006.01) **C12Q 1/68** (2006.01)
G01N 33/53 (2006.01) **G01N 37/00** (2006.01)

(86) International application number:
PCT/JP2009/064363

(87) International publication number:
WO 2010/018870 (18.02.2010 Gazette 2010/07)

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR
Designated Extension States:
AL BA RS

(30) Priority: **15.08.2008 JP 2008209210**

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(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

5 **[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.
10 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

15 **[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)

25 **[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.

30 **[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.

35 **[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 α 1 antitrypsin monoclonal antibody capable of specifically recognizing oxidized LDL- α 1 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.

40 **[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.

45 **[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 α 2-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)

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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: zutin 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
55	1	S19A3	2	XM_001129783 (PREDICTED similar to UM and senescent domain 1 (L00729260))

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(continued)

	Clone Name	SEQ ID NO.	Accession No.	Gene Name	
5	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)
10	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)
15	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)
20	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)
25	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)
30	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)
35	17	PA213	34	NM_006807	chromobox homolog 1 (HP1 beta homolog Drosophila) (CBX1)
	18	PA234	36	BC030642	PARK2 co-regulated (PACRG)

40 **[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.

45 **[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.

50 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.

55 **[0032]** As for the radioisotope, it is possible to use ^{125}I , ^3H , or such a substance for use in usual RIA (radioimmunoassay).

As for the fluorescent dye, it is possible to use fluorescein isothiocyanate (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.

5 [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.

10 [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.

15 [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.

20 [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.

25 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.

30 [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.

35 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.

40 [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.

45 [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.

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

55 [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.

5 **[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.

10 **[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.

15 **[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.

20 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.

25 Production Example

(Preparation of samples)

30 **[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 λ ZAP II phage vectors (STRATAGENE) recombined with a human microvascular endothelium-derived cDNA library were used.

45 (Expression cloning method)

[0056]

50 (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 ($\phi 15$ 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

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(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 tetrazolium) 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 ϕ 10 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 electrophoresis, 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 μ g/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 μ g/ml) overnight.

2) This was transferred to 20 ml of LB ampicillin and cultured for one hour, and was then added with IPTG to

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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 electrophoresed on a 10% polyacrylamide gel, and the protein was transferred to a nitro-cellulose 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.

5 **[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. 10 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.

20 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

30 **[0065]**

35

40

45

50

55

SEQUENCE LISTING

5 <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

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 Pro Arg His Gly Arg Tyr Leu Thr Val Ala Ala Val Phe Arg Gly Arg
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 Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Asn Val Gln Asn Lys
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 Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ser Ala Thr Phe Ile
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Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
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 Asp Gly Arg Ser Asp Glu Ser Ala Ala Lys Lys Pro Lys Trp Asp Asp
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 Glu Gln Arg Lys Gln Ala Phe Glu Glu Leu Arg Asp Asp Leu Val Glu
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 Glu Gly Arg Gln Lys Met Thr Ser Leu Ser Ser Cys Phe Ala Gln Leu
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 55 Tyr Gly Ala Arg Leu Ala Ala Lys Tyr Leu Asp Lys Glu Leu Ala Gly
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 20 Gly Leu His Val Gly Asp Ala Ile Leu Ala Val Asn Gly Val Asn Leu
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 30 Leu Tyr Leu Asp Glu Leu Glu Gly Gly Gly Asn Pro Gly Ala Ser Cys
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 Met Ala Phe Glu Gly Ile His Leu Pro Gln Ile Pro Gly Lys Leu Leu
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 Ser Ala Ala Arg Asn Gly Leu Leu Leu Leu Asn Leu Leu Leu Cys Asn
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 930 935 940
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 945 950 955 960
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25 **Claims**

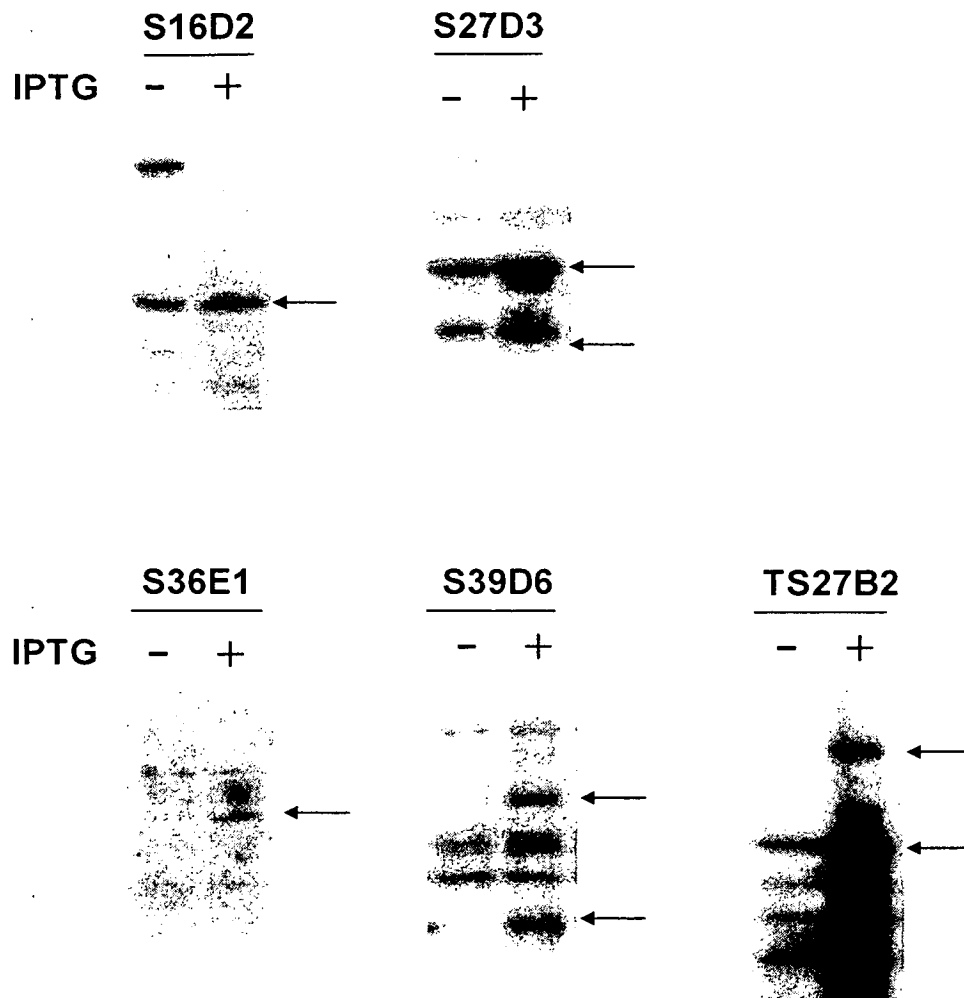
- 30 1. A polypeptide marker for diagnosing arteriosclerosis, which comprises a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 of the Sequence Listing, or a partial amino acid sequence thereof.
- 35 2. 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.
- 40 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.
- 45 4. An antibody specifically bindable to the polypeptide according to claim 1 as an antigen.
- 50 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.
- 55 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

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

- 5
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.
- 10
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.
- 15
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.
- 20
- 25
- 30
- 35
- 40
- 45
- 50
- 55

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
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> 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 "I" 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 04 November, 2009 (04.11.09)		Date of mailing of the international search report 17 November, 2009 (17.11.09)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		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.

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	EP2319924A1	公开(公告)日	2011-05-11
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	EP2319924B1 EP2319924A4		
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。

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 LINE, AND KIT FOR
 DIAGNOSIS OF ARTERIOSCLEROSIS

<130> SHIBE/P48247EP

<140> JP 09806761.4

<141> 2009-08-14

<150> JP 2008-209210

<151> 2008-08-15

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<400> 1

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 35 40 45

Leu Glu Lys Met Ala Glu Glu Leu Ala Lys Ala Cys Glu Asp Phe Val
 50 55 60

Gln Val Val Lys Ser Ser Gly Asn Thr Glu Ala Val Ser Val Ser Pro
 65 70 75 80

Val Ile Val Asn Ala Ala Leu Val Phe Gln Lys Ala Val Val Val Trp
 85 90 95

Val Phe Lys Ser Glu Lys His Gly Ile Val Asp Glu Val Leu Trp Gln
 100 105 110

Ile Cys Lys Ala Arg Val Asp Ile Ser Phe Ser Trp Arg Leu Thr Arg
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Leu Thr Cys Val Gly Thr Val Gly Val Thr Leu Ala Gly Lys Gln Gly
 130 135 140

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