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

(11) EP 2 653 871 A1

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

(43) Date of publication:
23.10.2013 Bulletin 2013/43

(21) Application number: **11849351.9**

(22) Date of filing: **14.06.2011**

(51) Int Cl.:
G01N 33/68 *(2006.01)* ***G01N 33/53*** *(2006.01)*
G01N 33/564 *(2006.01)*

(86) International application number:
PCT/JP2011/063563

(87) International publication number:
WO 2012/081271 (21.06.2012 Gazette 2012/25)

(84) Designated Contracting States:
AL 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 RS SE SI SK SM TR

(30) Priority: **15.12.2010 JP 2010279005**

(71) Applicant: **KayteeBio Co. & Ltd.**
Funabashi-shi, Chiba 273-0864 (JP)

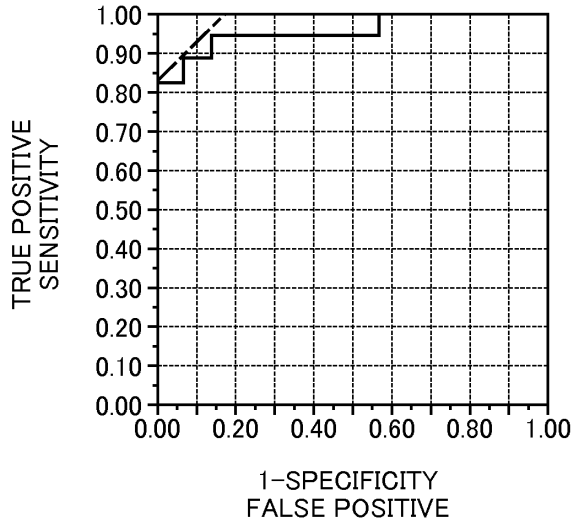
(72) Inventor: **TSUZAKA, Kensei**
Funabashi-shi
Chiba 2730864 (JP)

(74) Representative: **KATZAROV S.A.**
European Patent Attorneys
19, rue des Epinettes
1227 Genève (CH)

(54) NOVEL TEST METHOD FOR RHEUMATOID ARTHRITIS AND KIT FOR RHEUMATOID ARTHRITIS TEST

(57) Provided are: a novel test method for rheumatoid arthritis; and a kit for rheumatoid arthritis test, which is used in the novel test method for rheumatoid arthritis. A test method for rheumatoid arthritis according to the present invention is characterized by comprising a step for measuring the amount of talin in the plasma or serum of an animal subject. This measurement is carried out, for example, by an immunological method using an antibody which binds to talin. A kit for rheumatoid arthritis test according to the present invention is used for such a test method and contains, for example, a solid-phase carrier to which an antibody that binds to talin is affixed.

FIG. 1



EP 2 653 871 A1

Description

TECHNICAL FIELD

[0001] The present invention relates to a test method for rheumatoid arthritis, and a kit for rheumatoid arthritis test, which is used in such a test method.

BACKGROUND ART

[0002] Rheumatoid arthritis (RA) is a chronic inflammatory disease, in which the lesion occurs mainly in the synovial membrane tissue of the joint, and the prevalence rate of the disease is about 1% of the population. In rheumatoid arthritis, synovitis is found in the first stage, then cartilage or bone is gradually invaded, and the joint is destroyed and deformed in the advanced stage. Furthermore, the consequence of the symptom includes various examples such as an example in which arthritis undergoes remission and reoccurrence, repeatedly, then is completely cured, and an example in which arthritis rapidly progresses.

[0003] Diagnosis of rheumatoid arthritis is carried out mainly based on symptoms. Recently, however, attention has been paid to a diagnostic method using, as a marker, an autoantibody contained in the serum of a patient. As such an autoantibody, a rheumatoid factor (an autoantibody with respect to the deformed IgG), an anti-cyclic citrullinated peptide antibody (an anti-CCP antibody), and the like, are known (see Non-Patent Literature 1).

[0004] However, in previous reports, the sensitivity of the rheumatoid factor is 75 to 80%, the specificity thereof is 50 to 70%, and the sensitivity of the anti- CCP antibody is 50 to 75%, and the specificity is 85 to 95%, which are not necessarily satisfactory (see Non- Patent Literatures 2 and 3) .

Non-Patent Literature 1: Martinus A. M. et al., Arthritis Res. Ther., 4: 87-93, 2002
Non-Patent Literature 2: Avouac J. et al., Ann. Rheum. Dis. 65: 845-851, 2006
Non-Patent Literature 3: van Venrooij WJ. et al. Ann. N.Y. Acad. Sci. 1143: 268-285, 2008

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

[0005] The present invention aims to provide a test method for rheumatoid arthritis and a kit for rheumatoid arthritis test by searching novel markers that have not been previously known and being based on the found novel markers in the searching.

Means for Solving the Problems

[0006] In patients with rheumatoid arthritis, it is known that the peripheral blood lymphocyte is activated, so that cell adhesion with respect to the blood vessel endothelial cell is increased and at the same time, the lymphocyte migration is also increased, resulting in the infiltration of the lymphocyte to the outside of the blood vessel to cause various inflammations. In searching novel markers, the present inventor has focused on talin that is a high-molecular-weight cytoskeletal protein expressed in a concentrated manner mainly in regions in which the cell and the substrate are brought into contact with each other, in particular, in a cell adhesion region in the lymphocyte.

[0007] Talin is a protein formed of an N-terminal region having a molecular weight of 47 kDa and including an FERM region, and a C-terminal region having a molecular weight of 190 kDa and including one bundle of α-helix. The FERM region is classified into three sub-regions, that is, an F1 domain, an F2 domain, and an F3 domain, sequentially from the N-terminal side. In a living body, it is known that polypeptide in the N-terminal region, which is cleaved by Calpain, the F3 domain among them binds to an integrin β sub-unit increases signaling of the integrin from the inside of the cell to the outside of the cell, and thus the cell adhesion and cell migration are increased.

[0008] The present inventor has investigated the presence of talin in the plasma or the serum of a patient with rheumatoid arthritis. As a result, surprisingly, it is found that in a patient with rheumatoid arthritis, talin is dominantly present in the plasma or the serum. Furthermore, it is found that the amount of talin is significantly reduced when rheumatoid arthritis reaches a low disease activity or remission with the therapeutic agent for rheumatoid arthritis.

[0009] The present invention has been made based on such findings, and the present invention specifically includes the followings.

(1) A test method for rheumatoid arthritis, the method including a step of measuring an amount of talin in plasma or serum of an animal subject.

(2) The test method for rheumatoid arthritis descried in the above (1), further including a step of obtaining plasma or serum from blood collected from the animal subject.
(3) The test method for rheumatoid arthritis descried in the above (1) or (2), wherein the amount of talin in the plasma or the serum is measured by using an antibody which binds to talin.
(4) The test method for rheumatoid arthritis descried in any of the above (1) to (3), wherein the animal subject is a human subject.
(5) The test method for rheumatoid arthritis descried in any of the above (1) to (4), wherein the method is carried out for determining a diagnosis of rheumatoid arthritis or a treatment effect of a therapeutic agent for rheumatoid arthritis.
(6) A kit for rheumatoid arthritis test used for the test method for rheumatoid arthritis descried in any of the above (1) to (5).
(7) The kit for rheumatoid arthritis test descried in the above (6), including a solid-phase carrier to which an antibody that binds to talin is affixed.

Effects of the Invention

[0010] The present invention can provide a novel test method for rheumatoid arthritis and a kit for rheumatoid arthritis test to be used for such a test method.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

Fig. 1 is a graph showing an ROC curve of a diagnosis of rheumatoid arthritis (Example 1) by the Sandwich ELISA method using an H-18 antibody and an H-300 antibody.
Fig. 2 is a graph showing an ROC curve of a diagnosis of rheumatoid arthritis (Example 2) by the Sandwich ELISA method using an H-18 antibody and an M54246M antibody.
Fig. 3 is a graph showing an ROC curve of a diagnosis of rheumatoid arthritis (Comparative Example 1) using an anti-CCP antibody.

PREFERRED MODE FOR CARRYING OUT THE INVENTION

Test Method for Rheumatoid Arthritis

[0012] A test method for rheumatoid arthritis according to the present invention includes a step of measuring an amount of talin in the plasma or the serum of an animal subject. This test method may further include a step of obtaining the plasma or the serum from the blood collected from an animal subject.
[0013] The animal subject is not particularly limited as long as it can contract rheumatoid arthritis, and it can be selected depending upon purposes. Examples thereof include a human, a rat, a mouse, a dog, a cow, a cat, a rabbit, and a guinea pig, and preferable example is a human.
[0014] Furthermore, a method for obtaining the plasma or the serum is not particularly limited, it is possible to employ conventional methods, for example, a method for separating the plasma or the serum, which are obtained as specimen for clinical laboratory examination, from the blood. For example, the plasma can be obtained by taking the blood into an EDTA tube, a heparin tube, or the like, and the centrifuging thereof. Furthermore, the serum can be obtained by taking the blood into a test tube, and the centrifuging thereof.
[0015] With the test method for rheumatoid arthritis according to the present invention, an amount of talin in the thus obtained plasma or serum is measured. Herein, the "amount of talin" denotes an amount of protein of the talin. When talin has plurality of isoforms, any one of them may be measured. For example, in the case of human, two isoforms, that is, talin 1 and talin 2 are present. The mRNA sequence and the amino acid sequence of the talin 1 are shown in SEQ ID NOs: 1 and 2. Furthermore, the mRNA sequence and the amino acid sequence of the talin 2 are shown in SEQ ID NOs: 3 and 4.
[0016] The amount of talin in the plasma or the serum of an animal subject can be measured by an immunochemical method by using an antibody which binds to talin.
[0017] The antibody which binds to talin may be a polyclonal antibody or may be a monoclonal antibody, and, in some case, fragments of the antibody, for example, Fab', Fab, $F(ab')_2$ can be used. These antibodies can be prepared by conventionally known methods.
[0018] Examples of commercial products include an H-18 antibody (Santa Cruz Biotechnology Inc.), an H-300 antibody (Santa Cruz Biotechnology Inc.), a TA205 antibody (Abcam Inc.), and an M54246M antibody (Bio-design Co., Ltd.).

[0019] The amount of talin can be measured by employing well-known methods such as an enzyme immunoassay (EIA), a chemiluminescent immunoassay, a radioimmunoassay (RIA), a fluoro immunoassay, and a latex agglutination assay. Specific examples include a competitive assay using an antibody and label antigen, a Sandwich EIA method using combination of two types of antibodies, i.e., a monoclonal antibody or a polyclonal antibody (or a monoclonal antibody and a polyclonal antibody) whose recognition sites with respect to an antigen are different, and a latex agglutination assay using latex particles to which an antibody is affixed.

[0020] In these measurement methods, if necessary, an antigen or an antibody can be affixed to a solid-phase carrier. Examples of the solid-phase carrier include synthetic resin such as polystyrene, polyethylene, polypropylene, polyvinyl chloride, polyester, polyacrylic acid ester, nylon, polyacetal and fluorocarbon resin, polysaccharides such as cellulose and agarose, glass, metal, and the like. This solid-phase carrier can be formed in various shapes including a micro-plate shape, a spherical shape, a fibrous shape, a rod shape, a board shape, a container shape, a cell, a test tube, and the like.

[0021] In the above-mentioned immunochemical method, antibodies or antigens which are labeled may be used if necessary. Examples of such labels include radioisotope (^{124}I, ^{14}C, and ^{3}H), fluorescence materials (fluorescein isothiocyanate, and the like), and the like, in addition to enzymes (peroxidase, alkaline phosphatase, and the like), luminescent material (acridinium ester, isoluminol, luciferin, and the like). Besides, methods using combination of a biotin label and streptavidin can be employed.

[0022] As mentioned above, by measuring and quantifying the amount of talin in the plasma or the serum of an animal subject, it is possible to diagnose easily whether or not the subject has contracted rheumatoid arthritis. That is to say, when the amount of talin in the plasma or the serum is larger than a predetermined threshold, it can be determined that the subject has contracted rheumatoid arthritis. The predetermined threshold can be set, for example, based on a mean value and the like in the plasma or the serum in a control animal that has not contracted rheumatoid arthritis.

[0023] Furthermore, by measuring and quantifying the amount of talin before and after a therapeutic agent for rheumatoid arthritis is administered, a therapeutic effect by the therapeutic agent can be determined in a simple and easy manner. That is to say, when the amount of talin after the therapeutic agent for rheumatoid arthritis is administered is significantly lowered from the amount of talin before the administration, it can be determined that the therapeutic agent is effective.

[0024] Herein, the therapeutic agent for rheumatoid arthritis can include all the conventionally known therapeutic agents and all of therapeutic agents that will be developed in the future. Examples of the conventionally known therapeutic agent for rheumatoid arthritis include biological preparations, nonsteroidal anti- inflammatory agents (anti- inflammatory analgesic agents), steroid drugs, immunosuppressive agents, and the like.

[0025] Examples of the biological preparations include chimeric anti- TNF- α antibody preparations, soluble TNF receptors, complete human anti- TNF- α antibody preparations, anti- IL- 6- receptor antibody preparations, and the like. The nonsteroidal anti- inflammatory agents include prostaglandin production suppressing agents. They can reduce pain or swelling in the joint, but it is said that it is difficult to suppress the progress of the disease itself and suppress the destruction of the bone and the joint. The steroid drug has excellent anti- inflammation effect, so that it is used as specific medicine for rheumatoid arthritis. However, adverse effects thereof pose problems. The immunosuppressive agent reduces immunopathy of a rheumatoid arthritis patient, thereby suppressing the inflammation of rheumatoid arthritis, and is used for the purpose of introducing remission induction. Since this may be able to inhibit the progress of rheumatoid arthritis, this agent is also called disease modification anti- rheumatism drug. This is also called a slow acting anti-rheumatism drug because it takes a long time to exhibit an effect.

[0026] As mentioned above, there are various types of the therapeutic agents for rheumatoid arthritis, but the test method according to the present invention is also useful for determining the level of the effect of the therapeutic agent, and selecting the most effective therapeutic agent.

Kit for Rheumatoid Arthritis Test

[0027] A kit for rheumatoid arthritis test according to the present invention is provided for the use in a test method for rheumatoid arthritis according to the present invention. This diagnosis kit includes, for example, a solid-phase carrier to which an antibody that binds to talin is affixed. Furthermore, it may include a labeled secondary antibody, a coloring substrate, or the like.

EXAMPLES

[0028] Hereinafter, the present invention is described in detail with reference to Examples, but the present invention is not construed as being limited to the following description. Note here that in the following Examples 1 and 2, and Comparative Example 1, subjects include 17 patients with rheumatoid arthritis (RA patients), 14 controls (8 patients with osteoarthritis, 1 patient with systemic lupus erythematodes, 1 patient with diabetes, and 4 healthy subjects) . Furthermore, in the following Example 3, subjects are 5 RA patients.

Example 1

[0029] Blood of each subject is collected into an EDTA tube, and is centrifuged at 2500 rpm at room temperature for 10 min so as to obtain the plasma.

[0030] An amount of talin in the plasma was measured by a Sandwich ELISA method.

[0031] Firstly, an H- 18 antibody (Santa Cruz Biotechnology Inc.) recognizing the N- terminal of talin was diluted with a phosphate buffer solution (PBS) so that the concentration became 1 μg/mL, and added to a 96- well micro- plate at 100 μL/ well, which was incubated at 4°C overnight, followed by washing with 200 μL/ well of washing solution three times. Next, the plasma from each subject was added to the 96- well micro- plate at 100 μL/ well, which was incubated at 25°C for one hour, followed by washing with 200 μL/ well of washing solution three times. Next, an H- 300 antibody (Santa Cruz Biotechnology Inc.) as a primary antibody recognizing the N- terminal of talin was diluted with PBS so that the concentration became 2 μg/mL, and added to the 96- well micro- plate at 100 μL/ well, which was incubated at 25°C for one hour, followed by washing with 200 μL/ well of washing solution three times. Next, an HRP- labeled anti- goat IgG antibody (KPL) as a secondary antibody was diluted with PBS so that the concentration became 2 μg/mL, and added to the 96- well micro- plate at 100 μL/ well, which was incubated at 25°C for one hour, followed by washing with 200 μL/ well of washing solution three times.

[0032] Next, a substrate was added to a 96- well micro- plate at 100 μL/ well, which was incubated at 25°C for 15 min, and then, an OD value at wavelength of 630 nm was measured by using a microplate reader.

[0033] An ROC curve in Example 1 is shown in Fig. 1. As a result of the ROC analysis, an area below the ROC curve (AUC) in Fig. 1 was 0.954. Furthermore, whether being positive or negative based on the cut-off value of OD = 0.20 is shown in Table 1.

[Table 1]

		RA patient	Control	Total
H-300 antibody	Positive	14	0	14
	Negative	3	14	17
	Total	17	14	31

[0034] From the results, diagnosis of rheumatoid arthritis by the Sandwich ELISA method using the H-18 antibody and the H-300 antibody showed that the sensitivity was 14/17 x 100 = 82.4% and the specificity was 14/14 x 100 = 100%.

Example 2

[0035] The amount of talin in the plasma was measured by the Sandwich ELISA method by the same method as in Example 1 except that an M54246M antibody (Bio-design Co., Ltd.) recognizing the C-terminal of talin was used as a primary antibody.

[0036] An ROC curve in Example 2 is shown in Fig. 2. As a result of the ROC analysis, an area below the ROC curve (AUC) in Fig. 2 was 0.819. Furthermore, whether being positive or negative based on the cut-off value of OD = 0.05 is shown in Table 2.

[Table 2]

		RA patient	Control	Total
M54246M antibody	Positive	15	3	18
	Negative	2	11	13
	Total	17	14	31

[0037] From the results, diagnosis of rheumatoid arthritis by the Sandwich ELISA method using the H-18 antibody and the M54246M antibody showed that the sensitivity was 15/17 x 100 = 88.2% and the specificity was 11/14 x 100 = 78.6%.

Comparative Example 1

[0038] Blood from each subject was collected into a blood collecting tube for serum, and it was centrifuged at 2,500

rpm at room temperature for 10 min, and thus the serum was obtained. An anti-CCP antibody titer in the serum was measured by using a commercially available kit (MESACUP CCP manufactured by Medical & Biological laboratories Co., Ltd (MBL)) .

[0039] An ROC curve in Comparative Example 1 is shown in Fig. 3. As a result of the ROC analysis, an area below the ROC curve (AUC) in Fig. 3 was 0.838. Furthermore, whether being positive or negative based on the cut-off value of antibody titer = 6.60 is shown in Table 3.

[Table 3]

		RA patient	Control	Total
Anti-CCP antibody	Positive	11	1	12
	Negative	6	13	19
	Total	17	14	31

[0040] From the results, diagnosis of rheumatoid arthritis by using the anti-CCP antibody showed that the sensitivity was 11/17 x 100 = 64.7% and the specificity was 13/14 x 100 = 92.9%.

[0041] As is shown from the above-mentioned results, talin was dominantly present in the blood from a RA patient. Therefore, by measuring the amount of talin in the blood, it is possible to examine whether or not a subject contracted rheumatoid arthritis in a simple and easy manner. Moreover, the test method was more excellent in the sensitivity as compared with the existing method using anti-CCP antibody.

Example 3

[0042] A therapeutic effect of the therapeutic agent for rheumatoid arthritis for 5 RA patients was confirmed by measuring the amount of talin. The amount of talin was measured by measuring the OD value by the Sandwich ELISA method by using an H-18 antibody and an H-300 antibody as in Example 1. Furthermore, an amount of CRP and am amount of MMP-3 were measured by the same method as in usual clinical examination. Furthermore, the score of DAS (Disease Activity Score) 28 recommended by European League Against Rheumatism (EULAR) was calculated. The score of DAS28 of not less than 5.1 is determined to be high disease activity, the score of not less than 3.2 and less than 5.1 is determined to be middle disease activity, and the score of less than 3.2 is determined to be low disease activity. The results are shown in Table 4.

[Table 4]

Case 1: Male (ADA remarkable effective example)		Before (MTX treatment)	After (MTX + ADA treatment)
	Talin (0D value)	0. 068	0. 139
	CRP (mg/dL)	1. 74	0. 08
	MMP-3 (mg/mL)	60. 6	57. 4
	DAS28	5. 43	2. 62
Case 2: Female (SASP no effective example)		Before (non-treatment)	After (SASP treatment)
	Talin (0D value)	0. 258	0. 294
	CRP (mg/dL)	0. 36	0. 19
	MMP-3 (mg/mL)	70. 6	106. 6
	DAS28	5. 12	4. 21
Case 3: Female (IFX no effective example)		Before (MTX treatment)	After (MTX + IFX treatment)
	Talin (0D value)	0. 205	0. 223
	CRP (mg/dL)	2. 82	2. 68
	MMP-3 (mg/mL)	962. 1	523. 8
	DAS28	4. 87	3. 95

(continued)

Case 4: Female (ADA remarkable effective example)		Before (BUC treatment)	After (BUC + ADA treatment)
	Talin (0D value)	0. 258	0. 164
	CRP (mg/dL)	5. 01	0. 16
	MMP-3 (mg/mL)	323. 2	52. 2
	DAS28	4. 55	2. 45
Case 5: Female (TCZ no effective example)		Before (non-treatment)	After (TCZ treatment)
	Talin (0D value)	2. 093	1. 787
	CRP (mg/dL)	3. 83	2. 78
	MMP-3 (mg/mL)	117. 8	93. 1
	DAS28	5. 09	4. 50

[0043] A case 1 is an example in which when ADA (adalimumab) was used together in treatment with MTX (methotrexate), good responder (DAS28: 5.43 → 2.62) was shown based on the reactivity basis of EULAR. The amount of talin showed a high value (OD value: 0.568) when only MTX was used, but it showed a normal value (OD value: 0.139) when ADA was used together. On the other hand, the amount of MMP- 3 did not show significant reduction even when ADA was used together, which did not reflect the activity of rheumatoid arthritis.

[0044] A case 2 is an example in which also when treatment with SASP (salazosuffapyridine) was carried out, none responder (DAS28: 5.12 → 4.21) was shown based on the reactivity basis of EULAR. The amount of talin remained high (OD value: 0.258 → 0.294) even with SASP treatment. On the other hand, the CRP amount showed a normal value (0.19 mg/dL) after the SASP treatment was carried out, which did not reflect the pathology of rheumatoid arthritis.

[0045] A case 3 is an example in which none responder (DAS28: 4.87 → 3.95) was shown although IFX (infliximab) was used together with treatment with MTX (methotrexate). The amount of talin remained high (OD value: 0.205 → 0.223) even when treatment together with IFX was carried out.

[0046] A case 4 is an example in which good responder (DAS28: 4.55 → 2.45) was shown when ADA (adalimumab) was used together with treatment with BUC (bucillamine). The amount of talin showed a high value (OD value: 0.258) when only BUC was used, but it showed a normal value (OD value: 0.164) when ADA was used together.

[0047] A case 5 is an example in which none responder (DAS28: 5.09 → 4.50) was shown also when treatment using TCZ (tocilizumab) was carried out. The amount of talin remained high (OD value: 2.093 → 1.787) even with TCZ treatment.

[0048] As is shown from the above-mentioned results, the amount of talin in the blood correlates with the activity of rheumatoid arthritis, and it reflects the activity of rheumatoid arthritis more precisely as compared with the other factors such as CRP and MMP-3. Therefore, by measuring the amount of talin in the blood, it is possible to precisely determine the therapeutic effect of a therapeutic agent for rheumatoid arthritis.

SEQUENCE LISTING

<110> KayteeBio, Co.&Ltd.

<120> NOVEL TEST METHOD FOR RHEUMATOID ARTHRITIS AND KIT FOR RHEUMATOID ARTHRITIS TEST

<130> ATF-057PCT

<140> PCT/JP2011/063563

<141> 2011-06-14

<150> JP 2010-279005

<151> 2010-12-15

<160> 4

<210> 1
<211> 8187
<212> RNA
<213> Homo sapiens

<400> 1
cccgagaagc ggcggggcgg cgggccggcg ggcggggcgc agagccaggc agcgcaggta 60

tagccaggct ggagaaaaga agctgccacc atggttgcac tttcactgaa gatcagcatt 120

gggaatgtgg tgaagacgat gcagtttgag ccgtctacca tggtgtacga cgcctgccgc 180

atcattcgtg agcggatccc agaggcccca gctggtcctc ccagcgactt tgggctcttt 240

ctgtcagatg atgaccccaa aaagggtata tggctggagg ctgggaaagc tttggactac 300

tacatgctcc gaaatgggga cactatggag tacaggaaga aacagagacc cctgaagatc 360

cgtatgctgg atggaactgt gaagacgatc atggtggatg actctaagac tgtcactgac 420

atgctcatga ccatctgtgc ccgcattggc atcaccaatc atgatgaata ttcattggtt 480

cgagagctga tggaagagaa aaaggaggaa ataacaggga ccttaagaaa ggacaagaca 540

ttgctgcgag atgaaaagaa gatggagaaa ctaaagcaga aattgcacac agatgatgag 600

ttgaactggc tggaccatgg tcggacactg agggagcagg gtgtagagga gcacgagacg 660

ctgctgctgc ggaggaagtt cttttactca gaccagaatg tggattcccg ggaccctgta 720

cagctgaacc tcctgtatgt gcaggcacga gatgacatcc tgaatggctc ccaccctgtc 780

tcctttgaca aggcctgtga gtttgctggc ttccaatgcc agatccagtt tgggccccac 840

aatgagcaga agcacaaggc tggcttcctt gacctgaagg acttcctgcc caaggagtat 900

gtgaagcaga agggagagcg taagatcttc caggcacaca agaattgtgg gcagatgagt 960

gagattgagg ccaaggtccg ctacgtgaag ctagcccgtt ctctcaagac ttacggtgtc 1020

tccttcttcc tggtgaagga aaaaatgaaa gggaagaaca agctagtgcc caggcttctg 1080

ggcatcacca aggagtgtgt gatgcgagtg gatgagaaga ccaaggaagt gatccaggag 1140

tggaacctca ccaacatcaa acgctgggct gcgtctccca aaagcttcac cctggatttt 1200

ggagattacc aagatggcta ttactcagta cagacaactg aaggggagca gattgcacag 1260

ctcattgccg gctacatcga tatcatcctg aagaagaaaa aaagcaagga tcactttggg 1320

ctggaaggag atgaggagtc tactatgctg gaggactcag tgtcccccaa aaagtcaaca 1380
gtcctgcagc agcaatacaa ccgggtgggg aaagtggagc atggctctgt ggccctgcct 1440
gccatcatgc gctctggagc ctctggtcct gagaatttcc aggtgggcag catgcccccc 1500
gcccagcagc agattaccag cggccagatg caccgaggac acatgcctcc tctgacttca 1560
gcccagcagg cactcactgg aaccattaac tccagcatgc aggccgtgca ggctgcccag 1620
gccaccctgg atgactttga cactctgccg cctcttggcc aggatgctgc ctctaaggcc 1680
tggcgtaaaa acaagatgga tgaatcaaag catgagatcc actctcaggt agatgccatc 1740
acagctggta ctgcgtctgt ggtgaacctg acagcagggg accctgctga gacagactat 1800
accgcagtgg gctgtgcagt caccacaatc tcctccaacc tgacggagat gtcccgtggg 1860
gtgaagctgc tggctgcctt gctggaggac gaaggcggca gtggtcggcc cctgttgcag 1920
gcagcaaagg gccttgcggg agcagtgtca gaactgctgc gcagtgccca accagccagt 1980
gctgagcccc gtcagaacct gctgcaagca gctgggaacg tgggccaggc cagtggggag 2040
ctgttgcaac aaattgggga aagtgatact gacccccact tccaggatgc gctaatgcag 2100
ctcgccaaag ctgtggcaag tgctgcagct gccctggtcc tcaaggccaa gagtgtggcc 2160
cagcggacag aggactcggg acttcagacc caagttattg ctgcagcaac acagtgtgcc 2220
ctatccactt cccaactagt ggcctgtact aaggtggtgg cacctacaat cagctcacct 2280
gtctgccaag agcaactggt ggaggctgga cgactggtag ccaaagccgt ggagggctgt 2340
gtgtctgcct cccaggcagc tacagaggat gggcaactgt tgcgaggggt aggagcagca 2400
gccacagctg tcacccaggc cctaaatgag ctgctgcagc atgtgaaagc ccatgccaca 2460
ggggctgggc ctgctggccg ttatgaccag gctactgaca ccatcctaac cgtcactgag 2520
aacatcttta gctccatggg tgatgctggg gagatggtgg gacaggcccg catcctggcc 2580
caagccacat ctgacctggt caatgccatc aaggctgatg ctgaggggga aagtgatctg 2640
gagaactccc gcaagctctt aagtgctgcc aagatcctag ctgatgccac agccaagatg 2700
gtagaggctg ccaagggagc agctgcccac cctgacagtg aggagcagca gcagcggctg 2760
cgggaggcag ctgaggggct gcgcatggcc accaatgcag ctgcgcagaa tgccatcaag 2820
aaaaagctgg tgcagcgcct ggagcatgca gccaagcagg ctgcagcctc agccacacag 2880
accatcgctg cagctcagca cgcagcctct acccccaaag cctctgccgg cccccagccc 2940
ctgctggtgc agagctgcaa ggcagtggca gagcagattc cactgctggt gcagggcgtc 3000
cgaggaagcc aagcccagcc tgacagcccc agcgctcagc ttgccctcat tgctgccagc 3060
cagagcttcc tgcagccagg tgggaagatg gtggcagctg caaaggcctc agtgccaacg 3120
attcaggacc aggcttcagc catgcagctg agtcagtgtg ccaagaacct gggcaccgcg 3180
ctggctgaac tccggacggc tgcccagaag gctcaggaag catgtggacc tttggagatg 3240
gattctgcac tgagtgtggt acagaatcta gagaaagatc tacaggaagt gaaggcagca 3300
gctcgagatg gcaagcttaa acccttacct ggggagacaa tggagaagtg tacccaggac 3360
ctgggcaaca gcaccaaagc cgtgagctca gccatcgccc agctactggg agaggttgcc 3420

cagggcaatg agaattatgc aggtattgca gctcgggatg tggcaggtgg gctgcggtca 3480

ctggcccagg ccgctagggg agtcgctgca ctgacgtcag atcctgcagt gcaggccatt 3540

gtacttgata cggccagtga tgtgctggac aaggccagca gcctcattga ggaggcgaaa 3600

aaggcagctg gccatccagg ggaccctgag agccagcagc ggcttgccca ggtggctaaa 3660

gcagtgaccc aggctctgaa ccgctgtgtc agctgcctac ctggccagcg cgatgtggat 3720

aatgccctga gggcagttgg agatgccagc aagcgactcc tgagtgactc gcttcctcct 3780

agcactggga catttcaaga agctcagagc cggttgaatg aagctgctgc tgggctgaat 3840

caggcagcca cagaactggt gcaggcctct cggggaaccc ctcaggacct ggctcgagcc 3900

tcaggccgat ttggacagga cttcagcacc ttcctggaag ctggtgtgga gatggcaggc 3960

caggctccga gccaggagga ccgagcccaa gttgtgtcca acttgaaggg catctccatg 4020

tcttcaagca aacttcttct ggctgccaag gccctgtcca cggaccctgc tgcccctaac 4080

ctcaagagtc agctggctgc agctgccagg gcagtaactg acagcatcaa tcagctcatc 4140

actatgtgca cccagcaggc acccggccag aaggagtgtg ataacgccct gcgggaattg 4200

gagacggtcc gggaactcct ggagaaccca gtccagccca tcaatgacat gtcctacttt 4260

ggttgcctgg acagtgtaat ggagaactca aaggtgctgg gcgaggccat gactggcatc 4320

tcccaaaatg ccaagaacgg aaacctgcca gagtttggag atgccatttc cacagcctca 4380

aaggcacttt gtggcttcac cgaggcagct gcacaggctg catatctggt tggtgtctct 4440

gaccccaata gccaagctgg acagcaaggg ctagtggagc ccacacagtt tgcccgtgca 4500

aaccaggcaa ttcagatggc ctgccagagt ttgggagagc ctggctgtac ccaggcccag 4560

gtgctctctg cagccaccat tgtggctaaa cacacctctg cactgtgtaa cagctgtcgc 4620

ctggcttctg cccgtaccac caatcctact gccaagcgcc agtttgtaca gtcagccaag 4680

gaggtggcca acagcacagc taatcttgtc aagaccatca aggcgctaga tggggccttc 4740

acagaggaga accgtgccca gtgccgagca gcaacagccc ctctgctgga ggctgtggac 4800

aatctgagtg cctttgcgtc caaccctgag ttctccagca ttcctgccca gatcagccct 4860

gagggtcggg ctgccatgga gcccattgtg atctctgcca agacaatgtt agagagtgcc 4920

gggggactca tccagacagc ccgggccctc gcagtcaatc cccgggaccc cccgagctgg 4980

tcggtgctgg ccggccactc ccgtactgtc tcagactcca tcaagaagct aattacaagc 5040

atgagggaca aggctccagg gcagctggag tgtgaaacgg ccattgcagc tctgaacagt 5100

tgtctacggg acctagacca ggcttccctc gctgcagtca gccagcagct tgctccccgt 5160

gagggaatct ctcaagaggc cttgcacact cagatgctca ctgcagtcca agagatctcc 5220

catctcattg agccgctggc caatgctgcc cgggctgaag cctcccagct gggacacaag 5280

gtgtcccaga tggcgcagta ctttgagccg ctcaccctgg ctgcagtggg tgctgcctcc 5340

aagaccctga gccacccgca gcagatggca ctcctggacc agactaaaac attggcagag 5400

tctgccctgc agttgctata cactgccaag gaggctggtg gtaacccaaa gcaagcagct 5460

cacacccagg aagccctgga ggaggctgtg cagatgatga ccgaggccgt agaggacctg 5520
acaacaaccc tcaacgaggc agccagtgct gctggggtcg tgggtggcat ggtggactcc 5580
atcacccagg ccatcaacca gctagatgaa ggaccaatgg gtgaaccaga aggttccttc 5640
gtggattacc aaacaactat ggtgcggaca gccaaggcca ttgcagtgac cgttcaggag 5700
atggttacca agtcaaacac cagcccagag gagctgggcc ctcttgctaa ccagctgacc 5760
agtgactatg gccgtctggc ctcggaggcc aagcctgcag cggtggctgc tgaaaatgaa 5820
gagataggtt cccatatcaa acaccgggta caggagctgg gccatggctg tgccgctctg 5880
gtcaccaagg caggcgccct gcagtgcagc cccagtgatg cctacaccaa gaaggagctc 5940
atagagtgtg cccggagagt ctctgagaag gtctcccacg tcctggctgc gctccaggct 6000
gggaatcgtg gcacccaggc ctgcatcaca gcagccagcg ctgtgtctgg tatcattgct 6060
gacctcgaca ccaccatcat gttcgccact gctggcacgc tcaatcgtga gggtactgaa 6120
actttcgctg accaccggga gggcatcctg aagactgcga aggtgctggt ggaggacacc 6180
aaggtcctgg tgcaaaacgc agctgggagc caggagaagt tggcgcaggc tgcccagtcc 6240
tccgtggcga ccatcacccg cctcgctgat gtggtcaagc tgggtgcagc cagcctggga 6300
gctgaggacc ctgagaccca ggtggtacta atcaacgcag tgaaagatgt agccaaagcc 6360
ctgggagacc tcatcagtgc aacgaaggct gcagctggca aagttggaga tgaccctgct 6420
gtgtggcagc taaagaactc tgccaaggtg atggtgacca atgtgacatc attgcttaag 6480
acagtaaaag ccgtggaaga tgaggccacc aaaggcactc gggccctgga ggcaaccaca 6540
gaacacatac ggcaggagct ggcggttttc tgttccccag agccacctgc caagacctct 6600
accccagaag acttcatccg aatgaccaag ggtatcacca tggcaaccgc caaggccgtt 6660
gctgctggca attcctgtcg ccaggaagat gtcattgcca cagccaatct gagccgccgt 6720
gctattgcag atatgcttcg ggcttgcaag gaagcagctt accacccaga agtggcccct 6780
gatgtgcggc ttcgagccct gcactatggc cgggagtgtg ccaatggcta cctggaactg 6840
ctggaccatg tactgctgac cctgcagaag ccaagcccag aactgaagca gcagttgaca 6900
ggacattcaa agcgtgtggc tggttccgtc actgagctca tccaggctgc tgaagccatg 6960
aagggaacag aatgggtaga cccagaggac cccacagtca ttgctgagaa tgagctcctg 7020
ggagctgcag ccgccattga ggctgcagcc aaaaagctag agcagctgaa gccccgggcc 7080
aaacccaagg aggcagatga gtccttgaac tttgaggagc agatactaga agctgccaag 7140
tccattgcag cagccaccag tgcactggta aaggctgcgt cggctgccca gagagaacta 7200
gtggcccaag ggaaggtggg tgccattcca gccaatgcac tggacgatgg gcagtggtcc 7260
cagggcctca tttctgctgc ccggatggtg gctgcggcca ccaacaatct gtgtgaggca 7320
gccaatgcag ctgtacaagg ccatgccagc caggagaagc tcatctcatc agccaagcag 7380
gtagctgcct ccacagccca gctccttgtg gcctgcaagg tcaaggctga ccaggactcg 7440
gaggcaatga aacgacttca ggctgctggc aacgcagtga agcgagcctc agataatctg 7500
gtgaaagcag cacagaaggc tgcagccttt gaagagcagg agaatgagac agtggtggtg 7560

aaagagaaga tggttggcgg cattgcccag atcatcgcag cacaggaaga aatgcttcgg 7620

aaggaacgag agctggaaga ggcgcggaag aaactggccc agatccggca gcagcagtac 7680

aagtttctgc cttcagagct tcgagatgag cactaaagaa gcctcttcta tttaatgcag 7740

acccggccca gagactgtgc gtgccactac caaagccttc tgggctgtcg gggcccaacc 7800

tgcccaaccc cagcactccc caaagtgcct gccaaacccc agggcctggc cccgcccagt 7860

cccgcagtac atcccctgtc ccctccccaa ccccaagtgc cttcatgccc tagggccccc 7920

caagtgcctg cccctcccca gagtattaac gctccaagag tattattaac gctgctgtac 7980

ctcgatctga atctgccggg gccccagccc actccaccct gccagcagct tccagccagt 8040

ccccacagcc tcatcagctc tcttcaccgt tttttgatac tatcttcccc cacccccagc 8100

tacccatagg ggctgcagag ttataagccc caaacaggtc atgctccaat aaaaatgatt 8160

ctacctacaa aaaaaaaaaa aaaaaaa 8187

<210> 2
<211> 2541
<212> PRT
<213> Homo sapiens

<400> 2

```
Met Val Ala Leu Ser Leu Lys Ile Ser Ile Gly Asn Val Val Lys Thr
1               5                  10                  15

Met Gln Phe Glu Pro Ser Thr Met Val Tyr Asp Ala Cys Arg Ile Ile
            20                  25                  30

Arg Glu Arg Ile Pro Glu Ala Pro Ala Gly Pro Pro Ser Asp Phe Gly
        35                  40                  45

Leu Phe Leu Ser Asp Asp Asp Pro Lys Lys Gly Ile Trp Leu Glu Ala
    50                  55                  60

Gly Lys Ala Leu Asp Tyr Tyr Met Leu Arg Asn Gly Asp Thr Met Glu
65                  70                  75                  80

Tyr Arg Lys Lys Gln Arg Pro Leu Lys Ile Arg Met Leu Asp Gly Thr
                85                  90                  95

Val Lys Thr Ile Met Val Asp Asp Ser Lys Thr Val Thr Asp Met Leu
            100                 105                 110

Met Thr Ile Cys Ala Arg Ile Gly Ile Thr Asn His Asp Glu Tyr Ser
        115                 120                 125

Leu Val Arg Glu Leu Met Glu Glu Lys Lys Glu Glu Ile Thr Gly Thr
    130                 135                 140

Leu Arg Lys Asp Lys Thr Leu Leu Arg Asp Glu Lys Lys Met Glu Lys
145                 150                 155                 160

Leu Lys Gln Lys Leu His Thr Asp Asp Glu Leu Asn Trp Leu Asp His
                165                 170                 175

Gly Arg Thr Leu Arg Glu Gln Gly Val Glu Glu His Glu Thr Leu Leu
            180                 185                 190

Leu Arg Arg Lys Phe Phe Tyr Ser Asp Gln Asn Val Asp Ser Arg Asp
        195                 200                 205

Pro Val Gln Leu Asn Leu Leu Tyr Val Gln Ala Arg Asp Asp Ile Leu
```

```
    210                 215                 220

Asn Gly Ser His Pro Val Ser Phe Asp Lys Ala Cys Glu Phe Ala Gly
225                 230                 235                 240

Phe Gln Cys Gln Ile Gln Phe Gly Pro His Asn Glu Gln Lys His Lys
                245                 250                 255

Ala Gly Phe Leu Asp Leu Lys Asp Phe Leu Pro Lys Glu Tyr Val Lys
            260                 265                 270

Gln Lys Gly Glu Arg Lys Ile Phe Gln Ala His Lys Asn Cys Gly Gln
        275                 280                 285

Met Ser Glu Ile Glu Ala Lys Val Arg Tyr Val Lys Leu Ala Arg Ser
    290                 295                 300

Leu Lys Thr Tyr Gly Val Ser Phe Phe Leu Val Lys Glu Lys Met Lys
305                 310                 315                 320

Gly Lys Asn Lys Leu Val Pro Arg Leu Leu Gly Ile Thr Lys Glu Cys
                325                 330                 335

Val Met Arg Val Asp Glu Lys Thr Lys Glu Val Ile Gln Glu Trp Asn
            340                 345                 350

Leu Thr Asn Ile Lys Arg Trp Ala Ala Ser Pro Lys Ser Phe Thr Leu
        355                 360                 365

Asp Phe Gly Asp Tyr Gln Asp Gly Tyr Tyr Ser Val Gln Thr Thr Glu
    370                 375                 380

Gly Glu Gln Ile Ala Gln Leu Ile Ala Gly Tyr Ile Asp Ile Ile Leu
385                 390                 395                 400

Lys Lys Lys Lys Ser Lys Asp His Phe Gly Leu Glu Gly Asp Glu Glu
                405                 410                 415

Ser Thr Met Leu Glu Asp Ser Val Ser Pro Lys Lys Ser Thr Val Leu
            420                 425                 430

Gln Gln Gln Tyr Asn Arg Val Gly Lys Val Glu His Gly Ser Val Ala
        435                 440                 445

Leu Pro Ala Ile Met Arg Ser Gly Ala Ser Gly Pro Glu Asn Phe Gln
    450                 455                 460

Val Gly Ser Met Pro Pro Ala Gln Gln Gln Ile Thr Ser Gly Gln Met
465                 470                 475                 480

His Arg Gly His Met Pro Pro Leu Thr Ser Ala Gln Gln Ala Leu Thr
                485                 490                 495

Gly Thr Ile Asn Ser Ser Met Gln Ala Val Gln Ala Ala Gln Ala Thr
            500                 505                 510

Leu Asp Asp Phe Asp Thr Leu Pro Pro Leu Gly Gln Asp Ala Ala Ser
        515                 520                 525

Lys Ala Trp Arg Lys Asn Lys Met Asp Glu Ser Lys His Glu Ile His
    530                 535                 540

Ser Gln Val Asp Ala Ile Thr Ala Gly Thr Ala Ser Val Val Asn Leu
545                 550                 555                 560

Thr Ala Gly Asp Pro Ala Glu Thr Asp Tyr Thr Ala Val Gly Cys Ala
                565                 570                 575

Val Thr Thr Ile Ser Ser Asn Leu Thr Glu Met Ser Arg Gly Val Lys
```

580 585 590

Leu Leu Ala Ala Leu Leu Glu Asp Glu Gly Gly Ser Gly Arg Pro Leu
595 600 605

Leu Gln Ala Ala Lys Gly Leu Ala Gly Ala Val Ser Glu Leu Leu Arg
610 615 620

Ser Ala Gln Pro Ala Ser Ala Glu Pro Arg Gln Asn Leu Leu Gln Ala
625 630 635 640

Ala Gly Asn Val Gly Gln Ala Ser Gly Glu Leu Leu Gln Gln Ile Gly
645 650 655

Glu Ser Asp Thr Asp Pro His Phe Gln Asp Ala Leu Met Gln Leu Ala
660 665 670

Lys Ala Val Ala Ser Ala Ala Ala Ala Leu Val Leu Lys Ala Lys Ser
675 680 685

Val Ala Gln Arg Thr Glu Asp Ser Gly Leu Gln Thr Gln Val Ile Ala
690 695 700

Ala Ala Thr Gln Cys Ala Leu Ser Thr Ser Gln Leu Val Ala Cys Thr
705 710 715 720

Lys Val Val Ala Pro Thr Ile Ser Ser Pro Val Cys Gln Glu Gln Leu
725 730 735

Val Glu Ala Gly Arg Leu Val Ala Lys Ala Val Glu Gly Cys Val Ser
740 745 750

Ala Ser Gln Ala Ala Thr Glu Asp Gly Gln Leu Leu Arg Gly Val Gly
755 760 765

Ala Ala Ala Thr Ala Val Thr Gln Ala Leu Asn Glu Leu Leu Gln His
770 775 780

Val Lys Ala His Ala Thr Gly Ala Gly Pro Ala Gly Arg Tyr Asp Gln
785 790 795 800

Ala Thr Asp Thr Ile Leu Thr Val Thr Glu Asn Ile Phe Ser Ser Met
805 810 815

Gly Asp Ala Gly Glu Met Val Gly Gln Ala Arg Ile Leu Ala Gln Ala
820 825 830

Thr Ser Asp Leu Val Asn Ala Ile Lys Ala Asp Ala Glu Gly Glu Ser
835 840 845

Asp Leu Glu Asn Ser Arg Lys Leu Leu Ser Ala Ala Lys Ile Leu Ala
850 855 860

Asp Ala Thr Ala Lys Met Val Glu Ala Ala Lys Gly Ala Ala Ala His
865 870 875 880

Pro Asp Ser Glu Glu Gln Gln Gln Arg Leu Arg Glu Ala Ala Glu Gly
885 890 895

Leu Arg Met Ala Thr Asn Ala Ala Ala Gln Asn Ala Ile Lys Lys Lys
900 905 910

Leu Val Gln Arg Leu Glu His Ala Ala Lys Gln Ala Ala Ala Ser Ala
915 920 925

Thr Gln Thr Ile Ala Ala Ala Gln His Ala Ala Ser Thr Pro Lys Ala
930 935 940

Ser Ala Gly Pro Gln Pro Leu Leu Val Gln Ser Cys Lys Ala Val Ala

945 950 955 960

Glu Gln Ile Pro Leu Leu Val Gln Gly Val Arg Gly Ser Gln Ala Gln
965 970 975

Pro Asp Ser Pro Ser Ala Gln Leu Ala Leu Ile Ala Ala Ser Gln Ser
980 985 990

Phe Leu Gln Pro Gly Gly Lys Met Val Ala Ala Ala Lys Ala Ser Val
995 1000 1005

Pro Thr Ile Gln Asp Gln Ala Ser Ala Met Gln Leu Ser Gln Cys Ala
1010 1015 1020

Lys Asn Leu Gly Thr Ala Leu Ala Glu Leu Arg Thr Ala Ala Gln Lys
1025 1030 1035 1040

Ala Gln Glu Ala Cys Gly Pro Leu Glu Met Asp Ser Ala Leu Ser Val
1045 1050 1055

Val Gln Asn Leu Glu Lys Asp Leu Gln Glu Val Lys Ala Ala Ala Arg
1060 1065 1070

Asp Gly Lys Leu Lys Pro Leu Pro Gly Glu Thr Met Glu Lys Cys Thr
1075 1080 1085

Gln Asp Leu Gly Asn Ser Thr Lys Ala Val Ser Ser Ala Ile Ala Gln
1090 1095 1100

Leu Leu Gly Glu Val Ala Gln Gly Asn Glu Asn Tyr Ala Gly Ile Ala
1105 1110 1115 1120

Ala Arg Asp Val Ala Gly Gly Leu Arg Ser Leu Ala Gln Ala Ala Arg
1125 1130 1135

Gly Val Ala Ala Leu Thr Ser Asp Pro Ala Val Gln Ala Ile Val Leu
1140 1145 1150

Asp Thr Ala Ser Asp Val Leu Asp Lys Ala Ser Ser Leu Ile Glu Glu
1155 1160 1165

Ala Lys Lys Ala Ala Gly His Pro Gly Asp Pro Glu Ser Gln Gln Arg
1170 1175 1180

Leu Ala Gln Val Ala Lys Ala Val Thr Gln Ala Leu Asn Arg Cys Val
1185 1190 1195 1200

Ser Cys Leu Pro Gly Gln Arg Asp Val Asp Asn Ala Leu Arg Ala Val
1205 1210 1215

Gly Asp Ala Ser Lys Arg Leu Leu Ser Asp Ser Leu Pro Pro Ser Thr
1220 1225 1230

Gly Thr Phe Gln Glu Ala Gln Ser Arg Leu Asn Glu Ala Ala Ala Gly
1235 1240 1245

Leu Asn Gln Ala Ala Thr Glu Leu Val Gln Ala Ser Arg Gly Thr Pro
1250 1255 1260

Gln Asp Leu Ala Arg Ala Ser Gly Arg Phe Gly Gln Asp Phe Ser Thr
1265 1270 1275 1280

Phe Leu Glu Ala Gly Val Glu Met Ala Gly Gln Ala Pro Ser Gln Glu
1285 1290 1295

Asp Arg Ala Gln Val Val Ser Asn Leu Lys Gly Ile Ser Met Ser Ser
1300 1305 1310

Ser Lys Leu Leu Leu Ala Ala Lys Ala Leu Ser Thr Asp Pro Ala Ala

1315 1320 1325

Pro Asn Leu Lys Ser Gln Leu Ala Ala Ala Ala Arg Ala Val Thr Asp
1330 1335 1340

Ser Ile Asn Gln Leu Ile Thr Met Cys Thr Gln Gln Ala Pro Gly Gln
1345 1350 1355 1360

Lys Glu Cys Asp Asn Ala Leu Arg Glu Leu Glu Thr Val Arg Glu Leu
1365 1370 1375

Leu Glu Asn Pro Val Gln Pro Ile Asn Asp Met Ser Tyr Phe Gly Cys
1380 1385 1390

Leu Asp Ser Val Met Glu Asn Ser Lys Val Leu Gly Glu Ala Met Thr
1395 1400 1405

Gly Ile Ser Gln Asn Ala Lys Asn Gly Asn Leu Pro Glu Phe Gly Asp
1410 1415 1420

Ala Ile Ser Thr Ala Ser Lys Ala Leu Cys Gly Phe Thr Glu Ala Ala
1425 1430 1435 1440

Ala Gln Ala Ala Tyr Leu Val Gly Val Ser Asp Pro Asn Ser Gln Ala
1445 1450 1455

Gly Gln Gln Gly Leu Val Glu Pro Thr Gln Phe Ala Arg Ala Asn Gln
1460 1465 1470

Ala Ile Gln Met Ala Cys Gln Ser Leu Gly Glu Pro Gly Cys Thr Gln
1475 1480 1485

Ala Gln Val Leu Ser Ala Ala Thr Ile Val Ala Lys His Thr Ser Ala
1490 1495 1500

Leu Cys Asn Ser Cys Arg Leu Ala Ser Ala Arg Thr Thr Asn Pro Thr
1505 1510 1515 1520

Ala Lys Arg Gln Phe Val Gln Ser Ala Lys Glu Val Ala Asn Ser Thr
1525 1530 1535

Ala Asn Leu Val Lys Thr Ile Lys Ala Leu Asp Gly Ala Phe Thr Glu
1540 1545 1550

Glu Asn Arg Ala Gln Cys Arg Ala Ala Thr Ala Pro Leu Leu Glu Ala
1555 1560 1565

Val Asp Asn Leu Ser Ala Phe Ala Ser Asn Pro Glu Phe Ser Ser Ile
1570 1575 1580

Pro Ala Gln Ile Ser Pro Glu Gly Arg Ala Ala Met Glu Pro Ile Val
1585 1590 1595 1600

Ile Ser Ala Lys Thr Met Leu Glu Ser Ala Gly Gly Leu Ile Gln Thr
1605 1610 1615

Ala Arg Ala Leu Ala Val Asn Pro Arg Asp Pro Pro Ser Trp Ser Val
1620 1625 1630

Leu Ala Gly His Ser Arg Thr Val Ser Asp Ser Ile Lys Lys Leu Ile
1635 1640 1645

Thr Ser Met Arg Asp Lys Ala Pro Gly Gln Leu Glu Cys Glu Thr Ala
1650 1655 1660

Ile Ala Ala Leu Asn Ser Cys Leu Arg Asp Leu Asp Gln Ala Ser Leu
1665 1670 1675 1680

Ala Ala Val Ser Gln Gln Leu Ala Pro Arg Glu Gly Ile Ser Gln Glu

1685 1690 1695

Ala Leu His Thr Gln Met Leu Thr Ala Val Gln Glu Ile Ser His Leu
1700 1705 1710

Ile Glu Pro Leu Ala Asn Ala Ala Arg Ala Glu Ala Ser Gln Leu Gly
1715 1720 1725

His Lys Val Ser Gln Met Ala Gln Tyr Phe Glu Pro Leu Thr Leu Ala
1730 1735 1740

Ala Val Gly Ala Ala Ser Lys Thr Leu Ser His Pro Gln Gln Met Ala
1745 1750 1755 1760

Leu Leu Asp Gln Thr Lys Thr Leu Ala Glu Ser Ala Leu Gln Leu Leu
1765 1770 1775

Tyr Thr Ala Lys Glu Ala Gly Gly Asn Pro Lys Gln Ala Ala His Thr
1780 1785 1790

Gln Glu Ala Leu Glu Glu Ala Val Gln Met Met Thr Glu Ala Val Glu
1795 1800 1805

Asp Leu Thr Thr Thr Leu Asn Glu Ala Ala Ser Ala Ala Gly Val Val
1810 1815 1820

Gly Gly Met Val Asp Ser Ile Thr Gln Ala Ile Asn Gln Leu Asp Glu
1825 1830 1835 1840

Gly Pro Met Gly Glu Pro Glu Gly Ser Phe Val Asp Tyr Gln Thr Thr
1845 1850 1855

Met Val Arg Thr Ala Lys Ala Ile Ala Val Thr Val Gln Glu Met Val
1860 1865 1870

Thr Lys Ser Asn Thr Ser Pro Glu Glu Leu Gly Pro Leu Ala Asn Gln
1875 1880 1885

Leu Thr Ser Asp Tyr Gly Arg Leu Ala Ser Glu Ala Lys Pro Ala Ala
1890 1895 1900

Val Ala Ala Glu Asn Glu Glu Ile Gly Ser His Ile Lys His Arg Val
1905 1910 1915 1920

Gln Glu Leu Gly His Gly Cys Ala Ala Leu Val Thr Lys Ala Gly Ala
1925 1930 1935

Leu Gln Cys Ser Pro Ser Asp Ala Tyr Thr Lys Lys Glu Leu Ile Glu
1940 1945 1950

Cys Ala Arg Arg Val Ser Glu Lys Val Ser His Val Leu Ala Ala Leu
1955 1960 1965

Gln Ala Gly Asn Arg Gly Thr Gln Ala Cys Ile Thr Ala Ala Ser Ala
1970 1975 1980

Val Ser Gly Ile Ile Ala Asp Leu Asp Thr Thr Ile Met Phe Ala Thr
1985 1990 1995 2000

Ala Gly Thr Leu Asn Arg Glu Gly Thr Glu Thr Phe Ala Asp His Arg
2005 2010 2015

Glu Gly Ile Leu Lys Thr Ala Lys Val Leu Val Glu Asp Thr Lys Val
2020 2025 2030

Leu Val Gln Asn Ala Ala Gly Ser Gln Glu Lys Leu Ala Gln Ala Ala
2035 2040 2045

Gln Ser Ser Val Ala Thr Ile Thr Arg Leu Ala Asp Val Val Lys Leu

2050 2055 2060

Gly Ala Ala Ser Leu Gly Ala Glu Asp Pro Glu Thr Gln Val Val Leu
2065 2070 2075 2080

Ile Asn Ala Val Lys Asp Val Ala Lys Ala Leu Gly Asp Leu Ile Ser
2085 2090 2095

Ala Thr Lys Ala Ala Ala Gly Lys Val Gly Asp Asp Pro Ala Val Trp
2100 2105 2110

Gln Leu Lys Asn Ser Ala Lys Val Met Val Thr Asn Val Thr Ser Leu
2115 2120 2125

Leu Lys Thr Val Lys Ala Val Glu Asp Glu Ala Thr Lys Gly Thr Arg
2130 2135 2140

Ala Leu Glu Ala Thr Thr Glu His Ile Arg Gln Glu Leu Ala Val Phe
2145 2150 2155 2160

Cys Ser Pro Glu Pro Pro Ala Lys Thr Ser Thr Pro Glu Asp Phe Ile
2165 2170 2175

Arg Met Thr Lys Gly Ile Thr Met Ala Thr Ala Lys Ala Val Ala Ala
2180 2185 2190

Gly Asn Ser Cys Arg Gln Glu Asp Val Ile Ala Thr Ala Asn Leu Ser
2195 2200 2205

Arg Arg Ala Ile Ala Asp Met Leu Arg Ala Cys Lys Glu Ala Ala Tyr
2210 2215 2220

His Pro Glu Val Ala Pro Asp Val Arg Leu Arg Ala Leu His Tyr Gly
2225 2230 2235 2240

Arg Glu Cys Ala Asn Gly Tyr Leu Glu Leu Leu Asp His Val Leu Leu
2245 2250 2255

Thr Leu Gln Lys Pro Ser Pro Glu Leu Lys Gln Gln Leu Thr Gly His
2260 2265 2270

Ser Lys Arg Val Ala Gly Ser Val Thr Glu Leu Ile Gln Ala Ala Glu
2275 2280 2285

Ala Met Lys Gly Thr Glu Trp Val Asp Pro Glu Asp Pro Thr Val Ile
2290 2295 2300

Ala Glu Asn Glu Leu Leu Gly Ala Ala Ala Ala Ile Glu Ala Ala Ala
2305 2310 2315 2320

Lys Lys Leu Glu Gln Leu Lys Pro Arg Ala Lys Pro Lys Glu Ala Asp
2325 2330 2335

Glu Ser Leu Asn Phe Glu Glu Gln Ile Leu Glu Ala Ala Lys Ser Ile
2340 2345 2350

Ala Ala Ala Thr Ser Ala Leu Val Lys Ala Ala Ser Ala Ala Gln Arg
2355 2360 2365

Glu Leu Val Ala Gln Gly Lys Val Gly Ala Ile Pro Ala Asn Ala Leu
2370 2375 2380

Asp Asp Gly Gln Trp Ser Gln Gly Leu Ile Ser Ala Ala Arg Met Val
2385 2390 2395 2400

Ala Ala Ala Thr Asn Asn Leu Cys Glu Ala Ala Asn Ala Ala Val Gln
2405 2410 2415

Gly His Ala Ser Gln Glu Lys Leu Ile Ser Ser Ala Lys Gln Val Ala

2420 2425 2430

Ala Ser Thr Ala Gln Leu Leu Val Ala Cys Lys Val Lys Ala Asp Gln
2435 2440 2445

Asp Ser Glu Ala Met Lys Arg Leu Gln Ala Ala Gly Asn Ala Val Lys
2450 2455 2460

Arg Ala Ser Asp Asn Leu Val Lys Ala Ala Gln Lys Ala Ala Ala Phe
2465 2470 2475 2480

Glu Glu Gln Glu Asn Glu Thr Val Val Val Lys Glu Lys Met Val Gly
2485 2490 2495

Gly Ile Ala Gln Ile Ile Ala Ala Gln Glu Glu Met Leu Arg Lys Glu
2500 2505 2510

Arg Glu Leu Glu Glu Ala Arg Lys Lys Leu Ala Gln Ile Arg Gln Gln
2515 2520 2525

Gln Tyr Lys Phe Leu Pro Ser Glu Leu Arg Asp Glu His
2530 2535 2540

<210> 3
<211> 11650
<212> RNA
<213> Homo sapiens

<400> 3
atggtggccc tgtccttaaa gatttgtgtg cgccactgca acgtggtgaa gaccatgcag 60

tttgaaccat ctacagctgt gtacgatgcg tgtcgagtca ttcgggaacg ggtgcctgag 120

gcacaaactg ggcaagcttc tgactatgga ctctttcttt cggatgaaga cccgaggaaa 180

gggatttggc tggaagcggg cagaacactg gattactaca tgttgcggaa tggggatatt 240

ttggaatata aaaagaaaca gagacctcag aaaatccgga tgctggatgg atctgtgaag 300

acagtgatgg tggatgattc caagactgtg ggggagctcc tggtcactat ttgtagcaga 360

ataggaataa caaattatga agaatactcc ttaatccaag aaactattga agaaaagaaa 420

gaggaaggaa cgggcacact caaaaaagac aggacactgt tacgagatga gaggaaaatg 480

gagaagttga aggccaagct gcacacagat gatgacctaa attggctgga tcacagccga 540

acattcagag aacaaggagt agatgaaaac gaaacgttgc tgcttagacg gaagttcttt 600

tactctgatc agaatgtaga ttcgagagac cccgtgcagc tgaacttgct ttatgttcag 660

gcacgggatg acatcctgaa tggctctcac cctgtctcct tcgagaaagc ttgtgagttt 720

ggtggatttc aagcccagat acaatttgga cctcatgtgg aacataaaca caaacctgga 780

tttttagatc tgaaggaatt cctgcccaaa gaatatatca agcagagagg agctgaaaag 840

aggatctttc aggagcataa gaactgcgga gagatgagtg agatagaagc caaggtcaag 900

tacgtcaaac tcgcacggtc cctccgcaca tatggcgtgt ccttcttcct ggtgaaggag 960

aagatgaaag gcaagaacaa gctggtgcct cgcctgctgg ggatcaccaa agactcggtg 1020

atgcgcgtgg atgagaagac caaggaagtg ctgcaggagt ggcccctcac caccgtcaag 1080

cgctgggcag cctcacccaa gagcttcaca ctggattttg gggagtatca ggaaagctac 1140

tattcagtac aaaccaccga gggagagcag atatcccagc tgattgcagg ctacattgac 1200

atcatcctga aaaagaaaca aagtaaagat cgatttggac tagaaggtga tgaggagtca 1260
accatgttag aagagtccgt ttccccaaaa aagtccacca tcttgcagca gcagttcaac 1320
cggaccggga aggcagagca cggctcagtg gcgctgccgg ccgtgatgcg ctcgggctcc 1380
agcgggcctg agaccttcaa cgttggcagc atgccctcgc cacagcagca ggtcatggtt 1440
gggcagatgc accgaggcca catgccgcca ctgacctcag cccagcaggc cctgatgggg 1500
accatcaaca caagcatgca cgccgtccag caggcccagg atgatctcag tgagctcgac 1560
tcgctgccac ctctcggcca ggatatggca tctagggtat gggttcagaa caaagtcgac 1620
gaatccaaac acgaaatcca ttctcaagtt gatgctatca cggccggaac ggcttcagtt 1680
gttaacctca cagctggtga ccctgcagac actgactaca cagctgtggg atgtgcgatc 1740
accactattt cttccaacct gacggagatg tccaagggtg tgaagctatt ggccgccctc 1800
atggatgatg aggtgggcag cggggaggac ttgctcagag ctgccaggac cctcgctggg 1860
gcggtgtcag acttgctgaa agctgtgcag cctacttctg gagagcctcg acagacagtt 1920
ttgactgctg ctggcagcat cggacaagcc agtggggatc ttctgagaca gattggagag 1980
aatgagactg atgagcgatt ccaggatgtt ttaatgagtt tggccaaagc tgttgccaat 2040
gcagctgcca tgttggtact aaaggcaaag aatgttgccc aagtggccga agacactgtc 2100
ctacagaaca gggtaattgc tgctgccacc cagtgtgccc tctccacctc ccagcttgtg 2160
gcatgtgcca aggttgtgag ccccactatt agctcccctg tgtgccagga gcagctgatt 2220
gaagcaggga agctggtgga ccgctcggtg gagaactgtg tccgtgcctg ccaggcggcc 2280
actaccgata gtgagctcct gaagcaggtc agcgcagcgg ccagcgtggt cagccaggcc 2340
ctccatgatc tcctgcagca tgtgcggcag tttgccagcc gaggcgagcc catcggccgc 2400
tacgaccagg ctactgacac catcatgtgt gtcaccgaga gcatcttcag ctccatgggt 2460
gacgctggtg aaatggtgcg ccaggcgcgg gttctggccc aagccacatc agacctcgtc 2520
aatgccatga ggtcagatgc agaagccgaa atcgacatgg agaattcaaa gaagctcctg 2580
gcagcagcaa aactcttagc tgactccact gctcgcatgg tggaagctgc aaaggggggct 2640
gcagccaacc cagagaatga ggaccagcag caaaggctga gagaagctgc agaaggcctc 2700
cgggtagcaa ccaacgcagc tgcccagaat gctattaaga aaaaaattgt caaccgactg 2760
gaggttgcag ccaagcaggc cgcagcggca gccacacaga ccatcgccgc ctcccagaat 2820
gcagctgttt ccaacaagaa ccctgcggcc cagcagcagc tggtccagag ttgcaaggca 2880
gtggctgatc acatccctca gctggtccag ggagtgaggg ggagccaagc tcaagctgaa 2940
gacctgagtg cccagctggc tctcatcatc tccagccaga acttcctcca gcctggaagc 3000
aagatggtgt cctctgccaa agccgcagtg cccaccgtga gtgaccaggc cgcagccatg 3060
cagctgagcc agtgtgccaa gaacctggcc accagcttgg cggagctgcg taccgcctcg 3120
cagaaggccc atgaagcttg tggtccgatg gaaatcgatt cagctctgaa tacggtgcag 3180
acgcttaaga atgaactgca ggatgccaag atggcagccg tggagagcca gctgaagcca 3240
cttccagggg aaacgctgga aaaatgtgct caggacctgg gaagcacatc caaggcggtg 3300

ggctcctcca tggcacagct gctgacctgt gctgctcaag gcaacgaaca ctacacaggg 3360
gtggctgcta gagagacggc ccaagctctg aaaacactgg cccaggccgc ccgtggagtg 3420
gctgcatcga caaccgaccc cgcggccgcc catgccatgt tagattctgc tcgagacgtg 3480
atggagggct ccgccatgct cattcaagag gccaagcagg ccctgattgc acctggagat 3540
gcagagcgtc aacaaagact ggctcaggtg gctaaagccg tctcacactc cttgaataac 3600
tgcgtaaatt gcctccctgg gcagaaggat gtggacgtgg ccttgaagag catcggggag 3660
tccagcaaga agctgcttgt ggattcgcta cctccaagca cgaagccttt ccaggaagcc 3720
cagagtgaac tgaaccaggc agcagctgat ctgaaccagt ctgctgggga agtggtccat 3780
gccacccggg gccagagtgg agagttggct gcagcctctg gaaagttcag tgatgatttt 3840
gatgaattcc tcgatgctgg cattgagatg gctggccaag ctcagacaaa agaagaccag 3900
atccaagtga tagggaacct caagaatatc tcgatggcat ccagcaagct gctgttagct 3960
gccaagtctc tctctgtaga tccaggagct cccaatgcga aaaatctcct ggctgcagct 4020
gcaagagctg tgacagagag catcaatcaa ctcatcactc tgtgtaccca acaagctccg 4080
ggccagaaag agtgcgataa tgccctgcgg gagctcgaga ctgtgaaggg gatgttggac 4140
aatcctaatg aacctgttag tgacctctct tactttgact gcattgagag tgtgatggaa 4200
aactccaagg ttctgggtga atcgatggca gggatttcac agaatgccaa gaccggagac 4260
ctccctgcct ttggggaatg tgtggggatt gcatccaagg ctctctgtgg gctgacagag 4320
gctgcagccc aggctgcata cttggttggc atctctgatc caaacagcca ggcaggccac 4380
cagggcctgg tggaccccat ccagtttgcc agggctaacc aggccatcca gatggcatgc 4440
cagaacttgg tggaccctgg cagcagccca tcacaggtcc tgtcagccgc cacaattgtt 4500
gccaagcaca cgtcagcctt gtgcaatgcc tgccgcatcg cctcatccaa gacggccaac 4560
ccagtagcca agaggcactt cgtccagtca gccaaggaag tcgccaacag cactgccaac 4620
ctggtgaaga ccatcaaggc cctggatggg gatttctctg aagacaaccg caataagtgt 4680
cgcatcgcca ccgcaccctt gattgaagct gtggagaacc tgacagcgtt cgcctcaaac 4740
cctgagtttg tcagcattcc tgcccagatc agctccgagg gttcccaggc acaggaacca 4800
atcctggtct cagccaagac catgctggag agttcatcgt acctcattcg cactgcacgc 4860
tctctggcca tcaaccccaa agacccaccc acctggtctg tactggctgg acattcccat 4920
acagtgtccg actccatcaa gagtctcatc acttctatca gggacaaggc ccctggacag 4980
agggagtgtg attactccat cgatggcatc aaccggtgca tccgggacat cgagcaggcc 5040
tcgctggccg ccgtcagcca gagcctggcc acgagggacg acatctctgt ggaggccctg 5100
caggagcagc tgacttcggt ggtccaggaa atcggacacc ttatcgatcc catcgccaca 5160
gcggctcggg gagaagcagc tcagctggga cataaggtga cacaactggc aagctatttt 5220
gagcccttga tcttagccgc agttggtgtg gcctccaaga ttcttgatca tcagcagcag 5280
atgacggtgc tggaccagac caagactctc gcagagtctg ccttgcagat gttgtatgca 5340

gccaaagaag gtggcggaaa ccccaaggca caacacaccc atgacgccat cacagaggcc 5400
gcccagttga tgaaggaagc cgtggatgac atcatggtga cgctgaacga agctgccagt 5460
gaagtggggc tggttggggg catggtggac gccattgcag aagccatgag caagctggat 5520
gaaggcactc ctccagaacc aaagggaaca tttgtcgact atcagacgac tgtggttaaa 5580
tactccaaag ccattgcggt gacagctcag gaaatgatga ctaagtcggt tactaacccg 5640
gaggagttgg gaggactggc ttcacaaatg accagtgact atgggcacct ggctttccag 5700
ggccagatgg cagcagccac ggcggaacca gaggagatcg gattccagat tcgcactcgt 5760
gtgcaggacc tgggccacgg ctgtatcttc ctggtgcaga aggcaggggc cctccaggtc 5820
tgccccacag acagctacac caagagggag ctgatcgaat gcgcccgtgc cgtcacggaa 5880
aaggtctcct tggtgctctc ggctctccag gccgggaaca aaggaaccca ggcatgcatt 5940
acagccgcca ccgctgtgtc tgggatcatt gccgacctgg acaccaccat tatgtttgca 6000
acagcgggga cgctgaatgc agagaacagt gagaccttcg cagaccacag ggagaacatt 6060
ctcaagacgg ccaaggcctt ggtagaagac acgaaactac ttgtgtcagg agctgcgtcc 6120
actcctgaca agctggccca ggcggcccag tcctcagcag ccaccatcac ccagctcgca 6180
gaagtggtca agctgggggc agccagcctg ggctccgacg accccgagac ccaggtggtt 6240
ttgatcaatg ccatcaaaga tgtggccaag gccctttctg atctcatcag tgctaccaag 6300
ggagctgcca gcaagccagt ggacgaccct tccatgtacc agctcaaggg ggctgccaag 6360
gtgatggtga ccaatgtcac ctcgctcctc aagactgtaa aggcagtgga ggatgaggcc 6420
acccggggca ccagggcgct tgaggccaca attgaatgca taaagcagga gcttacggtg 6480
ttccagtcaa aagacgtacc tgaaaagaca tcatcacctg aagaatccat aaggatgacg 6540
aaaggcatca ccatggcaac agccaaagcc gtggcagctg ggaactcatg tagacaggag 6600
gacgtgattg ctactgccaa cctgagccgg aaagccgtgt cagatatgtt gacggcttgc 6660
aagcaagcat ccttccaccc cgatgtcagt gacgaggtga gaaccagagc cttgcgtttc 6720
gggacggagt gcacccttgg ctacttggac ctcctggagc acgtcttggt gattcttcag 6780
aaaccaaccc cagaattcaa gcagcagctg gccgctttct ccaagcgagt cgccggcgct 6840
gtgacagagc tcatccaggc ggcggaagcc atgaaaggaa cagagtgggt ggatccagaa 6900
gacccaactg tcattgcaga aacagagtta ctgggggctg cagcatccat cgaagctgct 6960
gctaagaagt tagagcaact gaagccaaga gcaaaaccaa aacaagcgga tgagaccctg 7020
gactttgagg aacagatctt ggaagctgct aaatccattg ctgctgccac aagcgccctg 7080
gtcaaatcgg cctcagcagc ccagagggag ctggtggccc aaggaaaggt gggctccatc 7140
cctgccaatg ctgcagacga cggacagtgg tcacaggggc tgatttctgc tgcccggatg 7200
gtggcggctg cgaccagcag tctctgtgag gcggccaatg cctccgttca gggacacgcc 7260
agcgaggaga agctcatctc atctgccaag caggtcgccg cttccacggc tcagctgctg 7320
gtggcctgca aggtgaaggc cgaccaggat tcagaggcca tgaggcggct acaggcggca 7380
ggaaatgctg tgaaaagagc ctcagacaat cttgtccgtg cagcccagaa ggcagctttt 7440

ggcaaagctg atgacgacga tgttgtagtg aaaaccaagt ttgtgggggg cattgctcag 7500

atcatcgccg cccaggaaga aatgctaaag aaagagcgag aactggaaga agcaaggaaa 7560

aaactggccc aaatccgcca gcagcagtat aagtttttac ccaccgagct gagggaagat 7620

gagggctaaa ggtgcgagcc cagatggcga gccccagggg atggccctgg ctgaactgga 7680

cagacagtgt tcctgagagg ctgggcactt agctggaaac cgcccacctc cctcccgggt 7740

gagcctggag ccctgcgtgc ttgttctcac atctctgtcc cgtcggcact ggctgcatga 7800

tcgtgatgtc acacggtaca atgtcctacc cacaactcct ctgccgcctc ccctcatgcc 7860

tcaccgtgtc tcaggagaga ggggtgcacg tttcatggac tgttaccaac aaagaaaagt 7920

cagtattatg ttgttctcag acactttggc ttttgttggt ccttctctta ggcctgctcc 7980

tggacctctt tatgatattg tgatagggaa aaaaatcatt gacgtcatag aatattcttc 8040

ttcctctcag gagaagacgg aagctggagt tggacatggt tcataaaagc cagaaacaca 8100

aacccgtgtg gactccggga gggtgactca ggtcctcctt ccatgtcttg agcactggct 8160

cacccagggg gtgaaaaatt cccgcccctg tttgcacgct ttcttgcctc cgtgtgtaag 8220

ctccttgtac aacccagacc catcttgtat tttgtggccc agaaaactga acgattattt 8280

tgttcctccg tagtccaaag ggcagagttg cggaaggccg tcggggcttg gtgagcaggg 8340

gctgtaatac agtctgtggg ctccttaccc tgcagaggct gtttcagctc acacagagtc 8400

atccacacaa acccacggct cccagttgac agtcagtgga atgctcgtct ccttagcgtc 8460

cagggtgggg attctgctgg aataaagagc ttcctcagtg actcatcttt aggtcccacg 8520

ctggtttctg tgccttcaga atggtcacaa gcccggattg gaaaggatct gcttacaaac 8580

ctgtcccctg tcctccaacc caaaacgcct ttttttctgt cttaatatcc agaaaatcta 8640

aatgcatcct aaaatcaatg tgaaccttta acaagatagt tttacttatt atcacataag 8700

acataagatg ttttcatttt ctggatgtca cacttccaga atttcatatt tttcccctct 8760

tttctttccc cttttcagag ccctcccata ggaagggaag ggcttgaatt tacccttaat 8820

ctgcaccttt agccaaggca gtgcatggaa gatgaatggc tcgtgggaca gaatctaatg 8880

ccagggagca ggagtgtttg aaagaattca tagtggggaa ggtaaaagtt aatggaagta 8940

catgattttc aaaactggta acagttaaag gcactcaccc tccgcctctc tctctctctc 9000

tctctctggt gtgctatcat gtcttggact ccatccacac tatagtttca aagttccact 9060

gacgggggaa agttggtgct ttggtcctcc gaagatgtca cctttcgacc ttgcccgatc 9120

ttgtttcacc agactctagc ccatgtcatg gttttaaaat acataaactt ctgacagctt 9180

cccatattta taagttactt ataagtgctg cacgtattag aatttttttt tttcagacca 9240

gtaaagttag agaaaagacg ctgtaaagga aaagcaagtg agagtatgtg taggacactg 9300

acagtgtgtg ggcaccagtt ctgaagagga ggggagctgc tggagcccta gcctgttggg 9360

gaaaagctgg cacactcttg gctcgccctc tttgagtgga gctgatccaa cacctcatgc 9420

ctgccttggc cggacactga gaggaggggc acacgtgctt ccagagacac tcaggagtca 9480

gaccccaatg ctcagagtca caatgtgttc atggcctcct gtaacaggac tctggggatc 9540
ccctctgtgg cccagcccac cccaccctct gctcttctat gctgtgccca gggcagctgc 9600
cctcttctgc ctgtgcccca tcccatcctg aaaacccagg accaaggcag gggcaggcag 9660
ccagttcttc caccttgcct cagagtcatt taaaaccttt actgcatttg ataccagaaa 9720
agcctccaga gacaaaccaa atgcaaaggc ctttccttta taactctaaa gaacaggcat 9780
cgaaagttta tttttgtagg agctatataa atactcacct ttctggagtc gtccagtgct 9840
gggagctttg gggagtttgg ttctcagtta tcacctggta tggtcccagt ttctcatctg 9900
tcctttcctc atccaccctg cacatgtgta tgtgaacggc ttcgtggccg gtgtggtggt 9960
ttctcatttc ataagatagt tgaagggcca tgccttgtct ggatgttatt taataggcac 10020
tactgcggtg tcctcagatg gtactgaggg ggccttctgg tccttcaaag gaaaataaca 10080
caggcatgag ttcatttggg agtgtgaact ttcagaacac ctaataagag agtggtgtca 10140
gagtaaaaac ggccccaggt ctggagcata gaagtgtatc tctgtgaaga gagagccggt 10200
gtgttgacat gtggttcttc tcacacccct ctactcctcg agggctttga atccttgggc 10260
tgatttttgt gccagaaatt gctgttcccg atggccaaaa ggggaacctg aactggattt 10320
cagaactgcc cagtgatttg aaaatttaga ttttacttgg gcctttcagg agtctttaga 10380
tagggatgct gaggtcatat ttagttcaat gaacagccct tgtttaagtt ttgccagtgt 10440
ccagccagct gtggccctgg ccatctgtgc aggcaggttc ctcaattcct ggttggccct 10500
gcagtcggtc aacacagtcc ctccaggtcg gctgcagagg cagctgccca gcctgcagtc 10560
tatgcacggg ccttaagaaa tgagctgcct gtagcctcac ggcatatgct tttatcaggg 10620
aaaacccttc gagcttcttc tgattctcac ctgcttgctt tctggctgtc ttagtcagtg 10680
tgtttacagg caactaaagc ctgttcctaa tttatcaaaa aattataacc aaaattcacc 10740
atagcctaag agagtaaacc ccacctccaa agtgatgcca aggccaaaac ctcatcaagg 10800
aaccagacac aggtcaaaag tggtgagcaa gccatggtct ctgctcctgg ggaactcaca 10860
cgctgacccc cgaggagcct tggtttcctc cctggcagat agtccccaga atcttctctc 10920
ccagctttga ggttctgggc tctggaaagg cctctgggat gctggcctta agatctcagc 10980
acagactatc agcatgttcc attctcagat tcctggagga aaggtaccct ctgttgacca 11040
aggggctggc tgcttctgag acttaccaac ccaagaaatt tggagacatt cccctcaggc 11100
taaaaggcag cggtccccag agttcagaaa gcaaaagatc ttgacaactg tgccagtagt 11160
ggctctggtc ctatctctcc acagtgctgg cctctgctgg ggaaggcatc tttcccaaag 11220
gtatccccaa gtaccatgtt gaaaatgtcc tcagtctgtt gctccatctt tctgagcctc 11280
tgcttggtat gtcatgttta tggtcactac ggatgagtgt gtgcagagtt tgggttgatt 11340
cttttaaatg ctacaaacaa gagctatttc ttttcaataa aaaaggtttg gattcggcct 11400
cttcctctga gcccacctcc cagccctcca gggagcatca gtgtacctga gtcactttgt 11460
ctgcatctct tcatcccaca aaacacgagg ctgggtctca ttcagcggcc tctcaccaac 11520
cttcaagatc cagaagaaaa caggaacgtt cagctctgcc ctgtgtcgta tctaatcaca 11580

tacattaatt tatctaacca cataagttat ttttttttat ttgccagaaa taaaccttta 11640

aaggaacaaa 11650

<210> 4
<211> 2542
<212> PRT
<213> Homo sapiens

<400> 4

```
Met Val Ala Leu Ser Leu Lys Ile Cys Val Arg His Cys Asn Val Val
1               5                  10                  15

Lys Thr Met Gln Phe Glu Pro Ser Thr Ala Val Tyr Asp Ala Cys Arg
            20                  25                  30

Val Ile Arg Glu Arg Val Pro Glu Ala Gln Thr Gly Gln Ala Ser Asp
        35                  40                  45

Tyr Gly Leu Phe Leu Ser Asp Glu Asp Pro Arg Lys Gly Ile Trp Leu
    50                  55                  60

Glu Ala Gly Arg Thr Leu Asp Tyr Tyr Met Leu Arg Asn Gly Asp Ile
65                  70                  75                  80

Leu Glu Tyr Lys Lys Lys Gln Arg Pro Gln Lys Ile Arg Met Leu Asp
                85                  90                  95

Gly Ser Val Lys Thr Val Met Val Asp Asp Ser Lys Thr Val Gly Glu
            100                 105                 110

Leu Leu Val Thr Ile Cys Ser Arg Ile Gly Ile Thr Asn Tyr Glu Glu
        115                 120                 125

Tyr Ser Leu Ile Gln Glu Thr Ile Glu Glu Lys Lys Glu Glu Gly Thr
    130                 135                 140

Gly Thr Leu Lys Lys Asp Arg Thr Leu Leu Arg Asp Glu Arg Lys Met
145                 150                 155                 160

Glu Lys Leu Lys Ala Lys Leu His Thr Asp Asp Asp Leu Asn Trp Leu
                165                 170                 175

Asp His Ser Arg Thr Phe Arg Glu Gln Gly Val Asp Glu Asn Glu Thr
            180                 185                 190

Leu Leu Leu Arg Arg Lys Phe Phe Tyr Ser Asp Gln Asn Val Asp Ser
        195                 200                 205

Arg Asp Pro Val Gln Leu Asn Leu Leu Tyr Val Gln Ala Arg Asp Asp
    210                 215                 220

Ile Leu Asn Gly Ser His Pro Val Ser Phe Glu Lys Ala Cys Glu Phe
225                 230                 235                 240

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

His Lys Pro Gly Phe Leu Asp Leu Lys Glu Phe Leu Pro Lys Glu Tyr
            260                 265                 270

Ile Lys Gln Arg Gly Ala Glu Lys Arg Ile Phe Gln Glu His Lys Asn
        275                 280                 285

Cys Gly Glu Met Ser Glu Ile Glu Ala Lys Val Lys Tyr Val Lys Leu
    290                 295                 300

Ala Arg Ser Leu Arg Thr Tyr Gly Val Ser Phe Phe Leu Val Lys Glu
```

305 310 315 320

Lys Met Lys Gly Lys Asn Lys Leu Val Pro Arg Leu Leu Gly Ile Thr
325 330 335

Lys Asp Ser Val Met Arg Val Asp Glu Lys Thr Lys Glu Val Leu Gln
340 345 350

Glu Trp Pro Leu Thr Thr Val Lys Arg Trp Ala Ala Ser Pro Lys Ser
355 360 365

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

Thr Thr Glu Gly Glu Gln Ile Ser Gln Leu Ile Ala Gly Tyr Ile Asp
385 390 395 400

Ile Ile Leu Lys Lys Lys Gln Ser Lys Asp Arg Phe Gly Leu Glu Gly
405 410 415

Asp Glu Glu Ser Thr Met Leu Glu Glu Ser Val Ser Pro Lys Lys Ser
420 425 430

Thr Ile Leu Gln Gln Gln Phe Asn Arg Thr Gly Lys Ala Glu His Gly
435 440 445

Ser Val Ala Leu Pro Ala Val Met Arg Ser Gly Ser Ser Gly Pro Glu
450 455 460

Thr Phe Asn Val Gly Ser Met Pro Ser Pro Gln Gln Gln Val Met Val
465 470 475 480

Gly Gln Met His Arg Gly His Met Pro Pro Leu Thr Ser Ala Gln Gln
485 490 495

Ala Leu Met Gly Thr Ile Asn Thr Ser Met His Ala Val Gln Gln Ala
500 505 510

Gln Asp Asp Leu Ser Glu Leu Asp Ser Leu Pro Pro Leu Gly Gln Asp
515 520 525

Met Ala Ser Arg Val Trp Val Gln Asn Lys Val Asp Glu Ser Lys His
530 535 540

Glu Ile His Ser Gln Val Asp Ala Ile Thr Ala Gly Thr Ala Ser Val
545 550 555 560

Val Asn Leu Thr Ala Gly Asp Pro Ala Asp Thr Asp Tyr Thr Ala Val
565 570 575

Gly Cys Ala Ile Thr Thr Ile Ser Ser Asn Leu Thr Glu Met Ser Lys
580 585 590

Gly Val Lys Leu Leu Ala Ala Leu Met Asp Asp Glu Val Gly Ser Gly
595 600 605

Glu Asp Leu Leu Arg Ala Ala Arg Thr Leu Ala Gly Ala Val Ser Asp
610 615 620

Leu Leu Lys Ala Val Gln Pro Thr Ser Gly Glu Pro Arg Gln Thr Val
625 630 635 640

Leu Thr Ala Ala Gly Ser Ile Gly Gln Ala Ser Gly Asp Leu Leu Arg
645 650 655

Gln Ile Gly Glu Asn Glu Thr Asp Glu Arg Phe Gln Asp Val Leu Met
660 665 670

Ser Leu Ala Lys Ala Val Ala Asn Ala Ala Ala Met Leu Val Leu Lys

675 680 685

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

Val Ile Ala Ala Ala Thr Gln Cys Ala Leu Ser Thr Ser Gln Leu Val
705 710 715 720

Ala Cys Ala Lys Val Val Ser Pro Thr Ile Ser Ser Pro Val Cys Gln
725 730 735

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

Cys Val Arg Ala Cys Gln Ala Ala Thr Thr Asp Ser Glu Leu Leu Lys
755 760 765

Gln Val Ser Ala Ala Ala Ser Val Val Ser Gln Ala Leu His Asp Leu
770 775 780

Leu Gln His Val Arg Gln Phe Ala Ser Arg Gly Glu Pro Ile Gly Arg
785 790 795 800

Tyr Asp Gln Ala Thr Asp Thr Ile Met Cys Val Thr Glu Ser Ile Phe
805 810 815

Ser Ser Met Gly Asp Ala Gly Glu Met Val Arg Gln Ala Arg Val Leu
820 825 830

Ala Gln Ala Thr Ser Asp Leu Val Asn Ala Met Arg Ser Asp Ala Glu
835 840 845

Ala Glu Ile Asp Met Glu Asn Ser Lys Lys Leu Leu Ala Ala Ala Lys
850 855 860

Leu Leu Ala Asp Ser Thr Ala Arg Met Val Glu Ala Ala Lys Gly Ala
865 870 875 880

Ala Ala Asn Pro Glu Asn Glu Asp Gln Gln Gln Arg Leu Arg Glu Ala
885 890 895

Ala Glu Gly Leu Arg Val Ala Thr Asn Ala Ala Ala Gln Asn Ala Ile
900 905 910

Lys Lys Lys Ile Val Asn Arg Leu Glu Val Ala Ala Lys Gln Ala Ala
915 920 925

Ala Ala Ala Thr Gln Thr Ile Ala Ala Ser Gln Asn Ala Ala Val Ser
930 935 940

Asn Lys Asn Pro Ala Ala Gln Gln Gln Leu Val Gln Ser Cys Lys Ala
945 950 955 960

Val Ala Asp His Ile Pro Gln Leu Val Gln Gly Val Arg Gly Ser Gln
965 970 975

Ala Gln Ala Glu Asp Leu Ser Ala Gln Leu Ala Leu Ile Ile Ser Ser
980 985 990

Gln Asn Phe Leu Gln Pro Gly Ser Lys Met Val Ser Ser Ala Lys Ala
995 1000 1005

Ala Val Pro Thr Val Ser Asp Gln Ala Ala Ala Met Gln Leu Ser Gln
1010 1015 1020

Cys Ala Lys Asn Leu Ala Thr Ser Leu Ala Glu Leu Arg Thr Ala Ser
1025 1030 1035 1040

Gln Lys Ala His Glu Ala Cys Gly Pro Met Glu Ile Asp Ser Ala Leu

1045 1050 1055

Asn Thr Val Gln Thr Leu Lys Asn Glu Leu Gln Asp Ala Lys Met Ala
1060 1065 1070

Ala Val Glu Ser Gln Leu Lys Pro Leu Pro Gly Glu Thr Leu Glu Lys
1075 1080 1085

Cys Ala Gln Asp Leu Gly Ser Thr Ser Lys Ala Val Gly Ser Ser Met
1090 1095 1100

Ala Gln Leu Leu Thr Cys Ala Ala Gln Gly Asn Glu His Tyr Thr Gly
1105 1110 1115 1120

Val Ala Ala Arg Glu Thr Ala Gln Ala Leu Lys Thr Leu Ala Gln Ala
1125 1130 1135

Ala Arg Gly Val Ala Ala Ser Thr Thr Asp Pro Ala Ala Ala His Ala
1140 1145 1150

Met Leu Asp Ser Ala Arg Asp Val Met Glu Gly Ser Ala Met Leu Ile
1155 1160 1165

Gln Glu Ala Lys Gln Ala Leu Ile Ala Pro Gly Asp Ala Glu Arg Gln
1170 1175 1180

Gln Arg Leu Ala Gln Val Ala Lys Ala Val Ser His Ser Leu Asn Asn
1185 1190 1195 1200

Cys Val Asn Cys Leu Pro Gly Gln Lys Asp Val Asp Val Ala Leu Lys
1205 1210 1215

Ser Ile Gly Glu Ser Ser Lys Lys Leu Leu Val Asp Ser Leu Pro Pro
1220 1225 1230

Ser Thr Lys Pro Phe Gln Glu Ala Gln Ser Glu Leu Asn Gln Ala Ala
1235 1240 1245

Ala Asp Leu Asn Gln Ser Ala Gly Glu Val Val His Ala Thr Arg Gly
1250 1255 1260

Gln Ser Gly Glu Leu Ala Ala Ala Ser Gly Lys Phe Ser Asp Asp Phe
1265 1270 1275 1280

Asp Glu Phe Leu Asp Ala Gly Ile Glu Met Ala Gly Gln Ala Gln Thr
1285 1290 1295

Lys Glu Asp Gln Ile Gln Val Ile Gly Asn Leu Lys Asn Ile Ser Met
1300 1305 1310

Ala Ser Ser Lys Leu Leu Leu Ala Ala Lys Ser Leu Ser Val Asp Pro
1315 1320 1325

Gly Ala Pro Asn Ala Lys Asn Leu Leu Ala Ala Ala Ala Arg Ala Val
1330 1335 1340

Thr Glu Ser Ile Asn Gln Leu Ile Thr Leu Cys Thr Gln Gln Ala Pro
1345 1350 1355 1360

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

Gly Met Leu Asp Asn Pro Asn Glu Pro Val Ser Asp Leu Ser Tyr Phe
1380 1385 1390

Asp Cys Ile Glu Ser Val Met Glu Asn Ser Lys Val Leu Gly Glu Ser
1395 1400 1405

Met Ala Gly Ile Ser Gln Asn Ala Lys Thr Gly Asp Leu Pro Ala Phe

1410 1415 1420

Gly Glu Cys Val Gly Ile Ala Ser Lys Ala Leu Cys Gly Leu Thr Glu
1425 1430 1435 1440

Ala Ala Ala Gln Ala Ala Tyr Leu Val Gly Ile Ser Asp Pro Asn Ser
1445 1450 1455

Gln Ala Gly His Gln Gly Leu Val Asp Pro Ile Gln Phe Ala Arg Ala
1460 1465 1470

Asn Gln Ala Ile Gln Met Ala Cys Gln Asn Leu Val Asp Pro Gly Ser
1475 1480 1485

Ser Pro Ser Gln Val Leu Ser Ala Ala Thr Ile Val Ala Lys His Thr
1490 1495 1500

Ser Ala Leu Cys Asn Ala Cys Arg Ile Ala Ser Ser Lys Thr Ala Asn
1505 1510 1515 1520

Pro Val Ala Lys Arg His Phe Val Gln Ser Ala Lys Glu Val Ala Asn
1525 1530 1535

Ser Thr Ala Asn Leu Val Lys Thr Ile Lys Ala Leu Asp Gly Asp Phe
1540 1545 1550

Ser Glu Asp Asn Arg Asn Lys Cys Arg Ile Ala Thr Ala Pro Leu Ile
1555 1560 1565

Glu Ala Val Glu Asn Leu Thr Ala Phe Ala Ser Asn Pro Glu Phe Val
1570 1575 1580

Ser Ile Pro Ala Gln Ile Ser Ser Glu Gly Ser Gln Ala Gln Glu Pro
1585 1590 1595 1600

Ile Leu Val Ser Ala Lys Thr Met Leu Glu Ser Ser Ser Tyr Leu Ile
1605 1610 1615

Arg Thr Ala Arg Ser Leu Ala Ile Asn Pro Lys Asp Pro Pro Thr Trp
1620 1625 1630

Ser Val Leu Ala Gly His Ser His Thr Val Ser Asp Ser Ile Lys Ser
1635 1640 1645

Leu Ile Thr Ser Ile Arg Asp Lys Ala Pro Gly Gln Arg Glu Cys Asp
1650 1655 1660

Tyr Ser Ile Asp Gly Ile Asn Arg Cys Ile Arg Asp Ile Glu Gln Ala
1665 1670 1675 1680

Ser Leu Ala Ala Val Ser Gln Ser Leu Ala Thr Arg Asp Asp Ile Ser
1685 1690 1695

Val Glu Ala Leu Gln Glu Gln Leu Thr Ser Val Val Gln Glu Ile Gly
1700 1705 1710

His Leu Ile Asp Pro Ile Ala Thr Ala Ala Arg Gly Glu Ala Ala Gln
1715 1720 1725

Leu Gly His Lys Val Thr Gln Leu Ala Ser Tyr Phe Glu Pro Leu Ile
1730 1735 1740

Leu Ala Ala Val Gly Val Ala Ser Lys Ile Leu Asp His Gln Gln Gln
1745 1750 1755 1760

Met Thr Val Leu Asp Gln Thr Lys Thr Leu Ala Glu Ser Ala Leu Gln
1765 1770 1775

Met Leu Tyr Ala Ala Lys Glu Gly Gly Gly Asn Pro Lys Ala Gln His

1780 1785 1790

Thr His Asp Ala Ile Thr Glu Ala Ala Gln Leu Met Lys Glu Ala Val
1795 1800 1805

Asp Asp Ile Met Val Thr Leu Asn Glu Ala Ala Ser Glu Val Gly Leu
1810 1815 1820

Val Gly Gly Met Val Asp Ala Ile Ala Glu Ala Met Ser Lys Leu Asp
1825 1830 1835 1840

Glu Gly Thr Pro Pro Glu Pro Lys Gly Thr Phe Val Asp Tyr Gln Thr
1845 1850 1855

Thr Val Val Lys Tyr Ser Lys Ala Ile Ala Val Thr Ala Gln Glu Met
1860 1865 1870

Met Thr Lys Ser Val Thr Asn Pro Glu Glu Leu Gly Gly Leu Ala Ser
1875 1880 1885

Gln Met Thr Ser Asp Tyr Gly His Leu Ala Phe Gln Gly Gln Met Ala
1890 1895 1900

Ala Ala Thr Ala Glu Pro Glu Glu Ile Gly Phe Gln Ile Arg Thr Arg
1905 1910 1915 1920

Val Gln Asp Leu Gly His Gly Cys Ile Phe Leu Val Gln Lys Ala Gly
1925 1930 1935

Ala Leu Gln Val Cys Pro Thr Asp Ser Tyr Thr Lys Arg Glu Leu Ile
1940 1945 1950

Glu Cys Ala Arg Ala Val Thr Glu Lys Val Ser Leu Val Leu Ser Ala
1955 1960 1965

Leu Gln Ala Gly Asn Lys Gly Thr Gln Ala Cys Ile Thr Ala Ala Thr
1970 1975 1980

Ala Val Ser Gly Ile Ile Ala Asp Leu Asp Thr Thr Ile Met Phe Ala
1985 1990 1995 2000

Thr Ala Gly Thr Leu Asn Ala Glu Asn Ser Glu Thr Phe Ala Asp His
2005 2010 2015

Arg Glu Asn Ile Leu Lys Thr Ala Lys Ala Leu Val Glu Asp Thr Lys
2020 2025 2030

Leu Leu Val Ser Gly Ala Ala Ser Thr Pro Asp Lys Leu Ala Gln Ala
2035 2040 2045

Ala Gln Ser Ser Ala Ala Thr Ile Thr Gln Leu Ala Glu Val Val Lys
2050 2055 2060

Leu Gly Ala Ala Ser Leu Gly Ser Asp Asp Pro Glu Thr Gln Val Val
2065 2070 2075 2080

Leu Ile Asn Ala Ile Lys Asp Val Ala Lys Ala Leu Ser Asp Leu Ile
2085 2090 2095

Ser Ala Thr Lys Gly Ala Ala Ser Lys Pro Val Asp Asp Pro Ser Met
2100 2105 2110

Tyr Gln Leu Lys Gly Ala Ala Lys Val Met Val Thr Asn Val Thr Ser
2115 2120 2125

Leu Leu Lys Thr Val Lys Ala Val Glu Asp Glu Ala Thr Arg Gly Thr
2130 2135 2140

Arg Ala Leu Glu Ala Thr Ile Glu Cys Ile Lys Gln Glu Leu Thr Val

2145 2150 2155 2160

Phe Gln Ser Lys Asp Val Pro Glu Lys Thr Ser Ser Pro Glu Glu Ser
2165 2170 2175

Ile Arg Met Thr Lys Gly Ile Thr Met Ala Thr Ala Lys Ala Val Ala
2180 2185 2190

Ala Gly Asn Ser Cys Arg Gln Glu Asp Val Ile Ala Thr Ala Asn Leu
2195 2200 2205

Ser Arg Lys Ala Val Ser Asp Met Leu Thr Ala Cys Lys Gln Ala Ser
2210 2215 2220

Phe His Pro Asp Val Ser Asp Glu Val Arg Thr Arg Ala Leu Arg Phe
2225 2230 2235 2240

Gly Thr Glu Cys Thr Leu Gly Tyr Leu Asp Leu Leu Glu His Val Leu
2245 2250 2255

Val Ile Leu Gln Lys Pro Thr Pro Glu Phe Lys Gln Gln Leu Ala Ala
2260 2265 2270

Phe Ser Lys Arg Val Ala Gly Ala Val Thr Glu Leu Ile Gln Ala Ala
2275 2280 2285

Glu Ala Met Lys Gly Thr Glu Trp Val Asp Pro Glu Asp Pro Thr Val
2290 2295 2300

Ile Ala Glu Thr Glu Leu Leu Gly Ala Ala Ala Ser Ile Glu Ala Ala
2305 2310 2315 2320

Ala Lys Lys Leu Glu Gln Leu Lys Pro Arg Ala Lys Pro Lys Gln Ala
2325 2330 2335

Asp Glu Thr Leu Asp Phe Glu Glu Gln Ile Leu Glu Ala Ala Lys Ser
2340 2345 2350

Ile Ala Ala Ala Thr Ser Ala Leu Val Lys Ser Ala Ser Ala Ala Gln
2355 2360 2365

Arg Glu Leu Val Ala Gln Gly Lys Val Gly Ser Ile Pro Ala Asn Ala
2370 2375 2380

Ala Asp Asp Gly Gln Trp Ser Gln Gly Leu Ile Ser Ala Ala Arg Met
2385 2390 2395 2400

Val Ala Ala Ala Thr Ser Ser Leu Cys Glu Ala Ala Asn Ala Ser Val
2405 2410 2415

Gln Gly His Ala Ser Glu Glu Lys Leu Ile Ser Ser Ala Lys Gln Val
2420 2425 2430

Ala Ala Ser Thr Ala Gln Leu Leu Val Ala Cys Lys Val Lys Ala Asp
2435 2440 2445

Gln Asp Ser Glu Ala Met Arg Arg Leu Gln Ala Ala Gly Asn Ala Val
2450 2455 2460

Lys Arg Ala Ser Asp Asn Leu Val Arg Ala Ala Gln Lys Ala Ala Phe
2465 2470 2475 2480

Gly Lys Ala Asp Asp Asp Asp Val Val Val Lys Thr Lys Phe Val Gly
2485 2490 2495

Gly Ile Ala Gln Ile Ile Ala Ala Gln Glu Glu Met Leu Lys Lys Glu
2500 2505 2510

Arg Glu Leu Glu Glu Ala Arg Lys Lys Leu Ala Gln Ile Arg Gln Gln

2515 2520 2525

Gln Tyr Lys Phe Leu Pro Thr Glu Leu Arg Glu Asp Glu Gly
2530 2535 2540

Claims

1. A test method for rheumatoid arthritis, the method comprising a step of measuring an amount of talin in plasma or serum of an animal subject.

2. The test method for rheumatoid arthritis according to claim 1, further comprising a step of obtaining plasma or serum from blood collected from the animal subject.

3. The test method for rheumatoid arthritis according to claim 1 or 2, wherein the amount of talin in the plasma or the serum is measured by using an antibody which binds to talin.

4. The test method for rheumatoid arthritis according to any one of claims 1 to 3, wherein the animal subject is a human subject.

5. The test method for rheumatoid arthritis according to any one of claims 1 to 4, wherein the method is carried out for diagnosing rheumatoid arthritis or determining a treatment effect of a therapeutic agent for rheumatoid arthritis.

6. A kit for rheumatoid arthritis test used for the test method for rheumatoid arthritis according to any one of claims 1 to 5.

7. The kit for rheumatoid arthritis test according to claim 6, comprising a solid-phase carrier to which an antibody that binds to talin is affixed.

FIG. 1

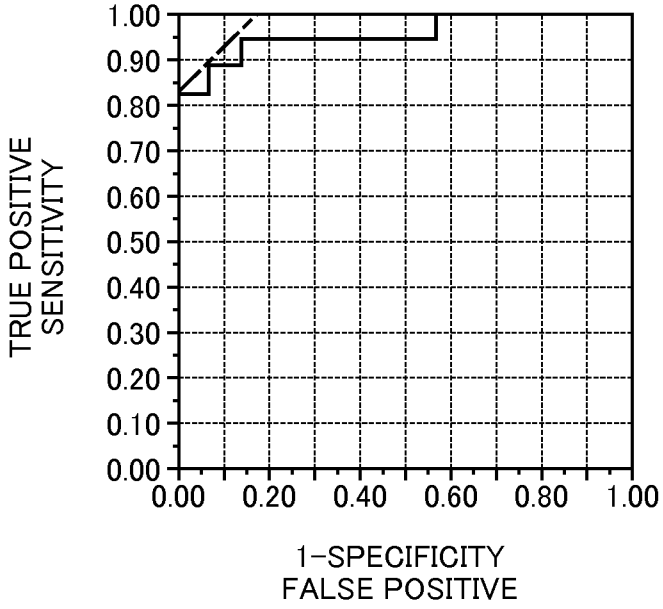

1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
TRUE POSITIVE
SENSITIVITY
0.00
0.20
0.40
0.60
0.80
1.00
1-SPECIFICITY
FALSE POSITIVE

FIG. 2

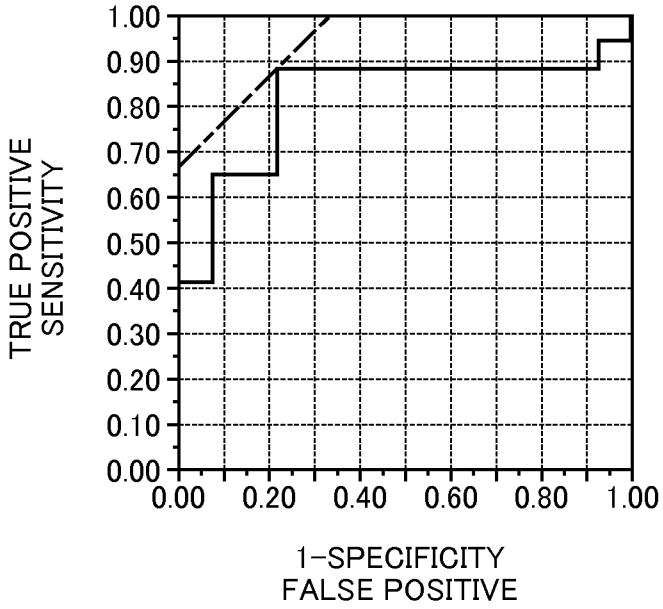
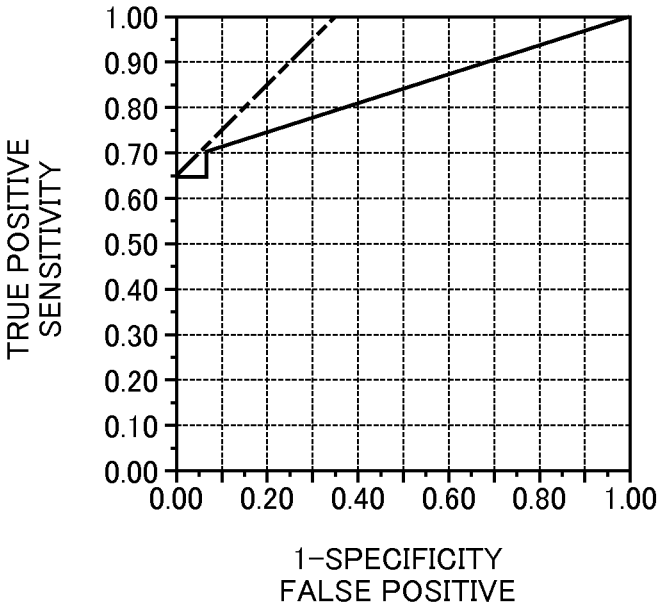

1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
TRUE POSITIVE
SENSITIVITY
0.00
0.20
0.40
0.60
0.80
1.00
1-SPECIFICITY
FALSE POSITIVE

FIG. 3


1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
TRUE POSITIVE
SENSITIVITY
0.00
0.20
0.40
0.60
0.80
1.00
1-SPECIFICITY
FALSE POSITIVE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/063563

A. CLASSIFICATION OF SUBJECT MATTER
G01N33/68(2006.01)i, *G01N33/53*(2006.01)i, *G01N33/564*(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)
G01N33/68, G01N33/53, G01N33/564

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 1996-2011
Kokai Jitsuyo Shinan Koho 1971-2011 Toroku Jitsuyo Shinan Koho 1994-2011

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
JSTPlus/JMEDPlus/JST7580(JDreamII), CAplus(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2009-510464 A (F. Hoffmann-LA Roche AG.), 12 March 2009 (12.03.2009), claim 1 & US 2007/0148704 A1 & EP 1934612 A & WO 2007/039280 A1 & CA 2623167 A & CN 101283278 A	1-5,7
A	JP 2003-024099 A (Applied Cell Biotechnologies, Inc.), 28 January 2003 (28.01.2003), claim 1 & WO 2003/006985 A1	1-5,7
A	JP 2004-012447 A (Takashi MURAMATSU), 15 January 2004 (15.01.2004), claim 1 (Family: none)	1-5,7

☒ 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
08 September, 2011 (08.09.11)	27 September, 2011 (27.09.11)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/063563

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2005-127754 A (Japan Science and Technology Agency), 19 May 2005 (19.05.2005), claim 4 (Family: none)	1-5,7
A	JP 2010-071833 A (Kyoto University), 02 April 2010 (02.04.2010), claim 1 (Family: none)	1-5,7
A	Hajime YOSHIFUJI, "Calpain · Calpastatin to Rheumatoid Arthritis", Rinsho Rheumatism, 30 September 2005 (30.09.2005), vol.17, no.3, pages 160 to 165	1-5,7
A	Martinus A.M. et al., Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value, Arthritis Res., 2002, Vol.4, P.87-93	1-5,7
A	Avouac J. et al., Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review, Ann. Rheum. Dis., 2006, Vol.65, P.845-851	1-5,7
A	Van Venrooij W.J. et al., Anti-CCP antibody, a marker for the early detection of rheumatoid arthritis, Ann. N. Y. Acad. Sci., 2008, Vol.1143, P.268-285	1-5,7

Form PCT/ISA/210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/063563

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.: 6
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:
Since it is unclear what components a kit for inspection of articular rheumatism set forth in claim 6 includes, the invention in claim 6 is lacks definiteness.

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:

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.:

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)) (July 2009)

REFERENCES CITED IN THE DESCRIPTION

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

Non-patent literature cited in the description

- **MARTINUS A. M. et al.** *Arthritis Res. Ther.,* 2002, vol. 4, 87-93 **[0004]**
- **AVOUAC J. et al.** *Ann. Rheum. Dis.,* 2006, vol. 65, 845-851 **[0004]**
- **VAN VENROOIJ WJ. et al.** *Ann. N.Y. Acad. Sci.,* 2008, vol. 1143, 268-285 **[0004]**

专利名称(译)	用于类风湿性关节炎的新型试验方法和用于类风湿性关节炎试验的试剂盒		
公开(公告)号	EP2653871A1	公开(公告)日	2013-10-23
申请号	EP2011849351	申请日	2011-06-14
[标]申请(专利权)人(译)	KAYTEE生物		
申请(专利权)人(译)	KAYTEEBIO CO.LTD及.		
当前申请(专利权)人(译)	KAYTEEBIO CO.LTD及.		
[标]发明人	TSUZAKA KENSEI		
发明人	TSUZAKA, KENSEI		
IPC分类号	G01N33/68 G01N33/53 G01N33/564		
CPC分类号	G01N33/564 G01N2333/4703 G01N2800/102		
优先权	2010279005 2010-12-15 JP		
其他公开文献	EP2653871B1 EP2653871A4		
外部链接	Espacenet		

摘要(译)

提供了一种新的类风湿性关节炎试验方法;用于类风湿性关节炎试验的试剂盒，用于类风湿性关节炎的新型试验方法。根据本发明的类风湿性关节炎的测试方法的特征在于包括测量动物受试者的血浆或血清中的踝蛋白量的步骤。该测量例如通过使用与踝蛋白结合的抗体的免疫学方法进行。根据本发明的用于类风湿性关节炎测试的试剂盒用于这种测试方法，并且包含例如固定有与踝蛋白结合的抗体的固相载体。

FIG. 1