

SPECIFICATION

RET INHIBITOR

TECHNICAL FIELD

[0001]

The present invention relates to a RET inhibitor, an inhibitor of RET tyrosine kinase, a prophylactic or therapeutic agent for diseases including cancers with a mutation in RET and their metastasis, a method for identifying a target patient, and the like, each of which comprises a tetracyclic compound or a salt thereof or a solvate thereof.

BACKGROUND ART

[0002]

Rearranged during transfection (RET) is a member of the receptor tyrosine kinases belonging to the cadherin superfamily (Surgery, 2007, vol. 141, p. 96-99). RET tyrosine kinase has a transmembrane region in the middle and has a tyrosine kinase region at the carboxyl-terminal side and an extracellular region at the amino-terminal side. It is known that there are three types of proteins due to differences in carboxyl-terminal splicing (TRENDS in Genetics, 2006, vol. 22, p. 627-636: Reference a). RET forms a dimer via a ligand/GFR complex to thereby phosphorylate and activate its own tyrosine (Reference a).

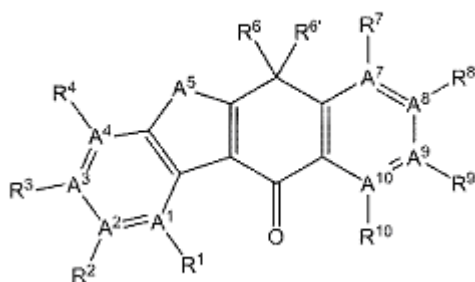
There are reports showing that RET will be involved in oncogenesis upon alterations (point mutation, chromosomal translocation, chromosomal inversion, gene amplification) in RET gene. For example, in thyroid medullary cancer, it is reported that a point mutation in RET gene results in the expression of RET tyrosine kinase with oncogenic ability (Reference a). Moreover, in thyroid papillary cancer, it is reported that RET gene is fused with another gene (e.g., coiled-coil domain containing 6 (CCDC6) gene or nuclear receptor coactivator 4 (NCOA4) gene) by chromosomal inversion or chromosomal translocation to cause the expression of fused tyrosine kinase RET/PTC with oncogenic ability (European Journal of Endocrinology, 2006, vol. 155, p. 645-653). Further, in non-small cell lung cancer,

it is reported that RET is fused with kinesin family protein 5B (KIF5B) gene, which is one of the molecules constituting motor protein complexes involved in intracellular microtubule transport, or with CCDC6 gene to cause non-small cell lung cancer by the constitutive tyrosine kinase activity of fused tyrosine kinase KIF5B-RET or CCDC6-RET with oncogenic ability (Nature Medicine. 2012, 18, p. 378-381, WO2012/014795). Moreover, it is reported that the fused tyrosine kinase NCOA4-RET or TRIM33-RET in which RET gene is fused with NCOA4 gene or TRIM33 (tripartite motif-containing 33) gene is present in non-small cell lung cancer patients (J Clin Oncol, 30 (35), Dec 10, 2012, p. 4352-9; and Cancer Discov 2013 Jun, 3 (6), Jun 2013, p. 630-5).

In view of the foregoing, compounds having an inhibitory effect against RET tyrosine kinase are very useful for cancer prevention and treatment.

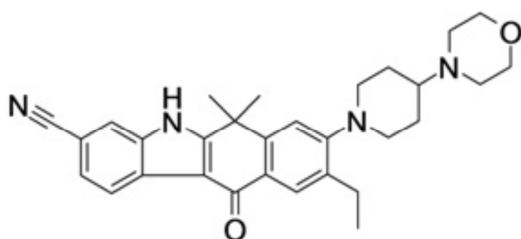
As inhibitory substances of RET tyrosine kinase, multi-kinase inhibitors such as sorafenib, sunitinib, XL184, vandetanib and ponatinib are reported to have a cell growth inhibitory effect against cell lines expressing KIF5B-RET (Non-patent Document 1: J Clin Oncol 30, 2012, suppl; Abstract no: 7510). Moreover, it is reported that two patients who have RET fusion gene-positive non-small cell lung cancer exhibited partial response to the multi-kinase inhibitor cabozantinib (Non-Patent Document 2: Cancer Discov, 3 (6), Jun 2013, p. 630-5).

On the other hand, a tetracyclic compound having the following general formula is reported as an inhibitor of anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase belonging to the insulin receptor family (Patent Document 1: WO2010/143664, Patent Document 2: WO2012/023597, Patent Document 3: Japanese Patent Laid-Open No. 2012-126711). This compound is useful as a therapeutic and/or prophylactic agent for tumors with a mutation in ALK gene.



(see the above patent gazette for details of substituents, etc.)

Moreover, it is reported that the following compound with a high concentration (1,000 nM) inhibits many kinases including RET in the Ambit Kinase Screening test (Non-Patent Document 3: Cancer Cell, 19 (5), p. 679-690, 2011, Supplemental Information):



However, there is no report showing that the tetracyclic compound found in Patent Document 1 and Non-patent Document 3 is useful as a therapeutic or prophylactic agent for cancers with a mutation in RET.

Moreover, it is reported that the ALK inhibitor crizotinib has no cell growth inhibitory activity against KIF5B-RET-expressing cells (Non-Patent Document 4: Nature Medicine. 2012, 18, p. 378-381).

[Document List]

[Patent Document]

[0003]

[Patent Document 1] WO2010/143664

[Patent Document 2] WO2012/023597

[Patent Document 3] JP2012-126711A

[Non-Patent Document]

[0004]

[Non-Patent Document 1] J Clin Oncol 30, 2012, suppl; Abstract no: 7510

[Non-Patent Document 2] Cancer Discov, 3 (6), Jun 2013, p. 630-5

[Non-Patent Document 3] Cancer Cell, 19 (5), p. 679-690, 2011, Supplemental Information

[Non-Patent Document 4] Nature Medicine. 2012, 18, p. 378-381

SUMMARY OF THE INVENTION

PROBLEM TO BE SOLVED BY THE INVENTION

[0005]

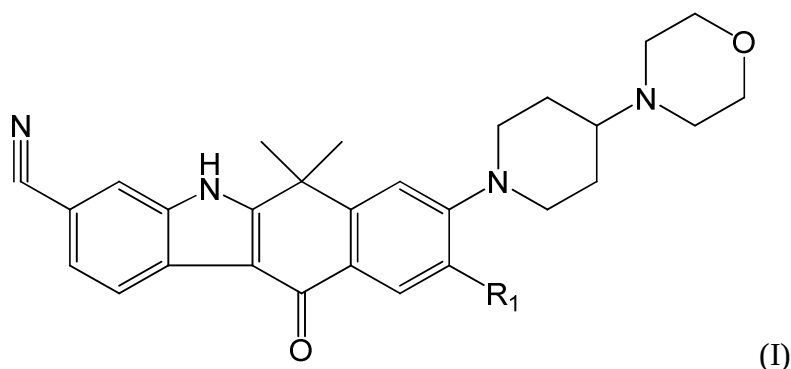
Cancers caused by a mutation in ALK gene and cancers caused by a mutation in RET gene differ in their mechanism of cancer development, the three-dimensional protein structure of their respective kinases, etc., and hence a specific therapeutic and/or prophylactic method is required for each cancer. In lung cancer, it is reported that a group of patients with a mutation in ALK gene does not overlap with a group of patients with a mutation in RET (Nat Med, 2012 Feb 12, 18 (3), 375-7). These patient groups are clearly distinguished from each other for treatment, and the patients in each group require a specific treatment and/or prevention method.

On the other hand, a compound which inhibits multiple kinases at the same time is known to show a lower therapeutic effect in some cases, because its effective therapeutic range is narrow. Thus, a drug which selectively inhibits a small number of kinases can be regarded as having desired properties in terms of therapeutic effect, and hence there is a demand for such a drug.

MEANS TO SOLVE THE PROBLEM

[0006]

As a result of extensive and intensive efforts made to solve the above problem, the inventors of the present invention have found, ahead of others, that a tetracyclic compound represented by the following formula (I) or a salt thereof or a solvate thereof has not only inhibitory activity against ALK but also potent inhibitory activity against RET, selectively inhibits RET, is useful for treatment and prevention of diseases including cancers with a mutation in RET and their metastasis, and also has high therapeutic efficacy on these diseases. This finding led to the completion of the present invention.



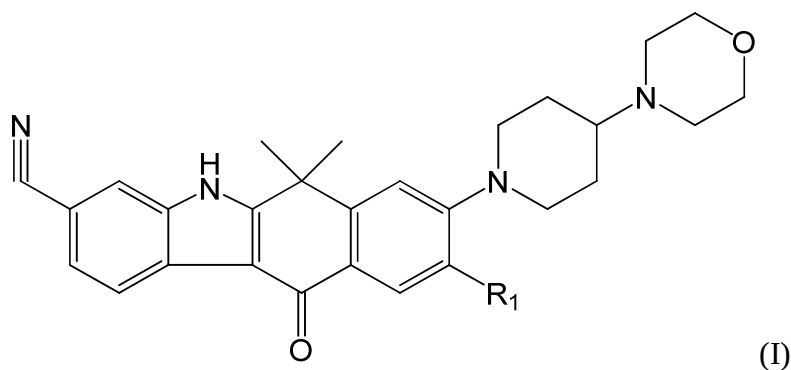
wherein R₁ is a C₁₋₆ alkyl group.

Namely, according to one aspect of the present invention, the present invention is directed to a therapeutic or prophylactic agent for cancers with a mutation in RET and their metastasis, which comprises a tetracyclic compound shown blow or a salt thereof, etc. According to another aspect, the present invention provides a method for identifying a cancer or a target patient responsive to treatment with the above compound or the like.

[0007]

More specifically, the present invention is as follows.

[1] A therapeutic and/or prophylactic agent for a tumor with a mutation in RET or for metastasis of the tumor, which comprises a compound represented by formula (I), a salt thereof or a solvate thereof as an active ingredient:



wherein R₁ is a C₁₋₆ alkyl group.

[2] The therapeutic and/or prophylactic agent according to [1] above, wherein the tumor is selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, brain tumor, neuroblastoma, glioma, thyroid cancer, myelodysplastic syndrome, head and neck cancer, esophageal

cancer, gastric cancer, colorectal cancer, , breast cancer, ovarian cancer, lung cancer, pancreatic cancer, liver cancer, gallbladder cancer, skin cancer, malignant melanoma, kidney cancer, renal pelvic and ureteral cancer, bladder cancer, uterine cancer, testicular cancer, prostate cancer, and tumors metastasized from these tumors.

[3] The therapeutic and/or prophylactic agent according to [1] or [2] above, wherein the tumor is thyroid cancer or lung cancer.

[4] The therapeutic and/or prophylactic agent according to any one of [1] to [3] above, wherein the tumor is thyroid medullary cancer or non-small cell lung cancer.

[4-1] The therapeutic and/or prophylactic agent according to [1] to [4] above, wherein the tumor is a tumor confirmed to show activated RET tyrosine kinase in the tumor tissue.

[4-2] The therapeutic and/or prophylactic agent according to [1] to [4] above, wherein the tumor is a tumor with a mutation which induces activation of RET tyrosine kinase.

[4-2-1]The therapeutic and/or prophylactic agent according to any one of [1] to [4-2] above, wherein the tumor is a tumor with (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) a fusion gene of RET and/or a fusion protein of RET.

[4-2-2]The therapeutic and/or prophylactic agent according to any one of [1] to [4-2] above, wherein the tumor is a tumor with a fusion gene of RET and/or a fusion protein of RET.

[4-2-3]The therapeutic and/or prophylactic agent according to any one of [1] to [4-2] and [4-2-2] above, wherein the tumor is a tumor with KIF5B-RET, CCDC6-RET, NCOA4-RET or TRIM33-RET.

[4-3] The therapeutic and/or prophylactic agent according to [1] to [4-2] above, wherein the tumor is a tumor with (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[0008]

[5] The therapeutic and/or prophylactic agent according to any one of [1] to [4-2] above, wherein the tumor is a tumor with a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[5-1] The therapeutic and/or prophylactic agent according to [5] above, wherein the another gene and protein are the gene and protein of KIF5B, CCDC6 or NCOA4 or TRIM33.

[5-2] The therapeutic and/or prophylactic agent according to [5] or [5-1] above, wherein the fusion gene and protein comprises the tyrosine kinase domain of RET gene or protein and the coiled-coil domain of another gene or protein.

[5-2-1] The therapeutic and/or prophylactic agent according to any one of [5] to [5-2] above, wherein a polypeptide constituting the RET protein and a polynucleotide constituting the RET gene are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 3 or 4;
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the polypeptide shown in SEQ ID NO: 3 or 4; and
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 3 or 4.

[5-2-2] The therapeutic and/or prophylactic agent according to [5-1] or [5-2-1] above, wherein a polypeptide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 proteins and a polynucleotide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 genes are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

(1) the polypeptide constituting the KIF5B protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 30,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 30, or
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 30;

(2) the polypeptide constituting the CCDC6 protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 31,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 31, or
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 31;

(3) the polypeptide constituting the NCOA4 protein is

- (a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42, or
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42; and

(4) the polypeptide constituting the TRIM33 protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 45 or 46,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 45 or 46, or
- (c) a polypeptide consisting of amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 45 or 46.

[5-2-3]The therapeutic and/or prophylactic agent according to [4-2-2], [5] or [5-2] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (b) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24, or a polypeptide comprising an amino acid

sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(c) a polypeptide comprising an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;

(e) a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 27 or 28, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28; and

(f) a polypeptide comprising an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28.

[5-2-4]The therapeutic and/or prophylactic agent according to [4-2-2], [5] or [5-2] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

(a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(b) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which carries activated tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;

(c) a polypeptide which comprises an amino acid sequence with 90% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;

(d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;

(e) a polypeptide which comprises the amino acid sequence shown in SEQ ID NO: 27 or 28 and which carries activated RET tyrosine kinase, or a polypeptide

which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity; and

(f) a polypeptide which comprises an amino acid sequence with 90% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity.

[5-3] The therapeutic and/or prophylactic agent according to [5-2] above, wherein the fusion gene is any of (a) to (d) shown below:

(a) a fusion gene which comprises a polynucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14;

(b) a fusion gene consisting of a polynucleotide which hybridizes under stringent conditions to DNA consisting of a nucleotide sequence complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14 and which encodes a polypeptide having tyrosine kinase activity;

(c) a fusion gene which comprises a polynucleotide encoding a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24; or

(d) a fusion gene comprising a polynucleotide encoding a polypeptide which has substitution, deletion or insertion of one or more (e.g., several tens, 1 to 10, 1 to 5, 1 to 3) amino acids in a polypeptide having an amino acids sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity.

[0009]

[6] The therapeutic and/or prophylactic agent according to any one of [1] to [4-2] above, wherein the tumor is a tumor with a point mutation in RET gene and/or protein.

[6-1] The therapeutic and/or prophylactic agent according to [6] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A, 2600G, 2861T or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[6-1-1] The therapeutic and/or prophylactic agent according to [6] or [6-1] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G,

2562A or 2861T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[6-2] The therapeutic and/or prophylactic agent according to [6] or [6-1] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2494G, 2600G or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[6-3] The therapeutic and/or prophylactic agent according to [6] or [6-1] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T, 2600G>A, 2600G>C, 2861T>G or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[6-3-1] The therapeutic and/or prophylactic agent according to [6], [6-1] or [6-3] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T or 2861T>G in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[6-4] The therapeutic and/or prophylactic agent according to [6], [6-1], [6-2] or [6-3] above, wherein the point mutation is 2091G>T, 2494G>C, 2600G>A or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[6-5] The therapeutic and/or prophylactic agent according to [6] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[6-5-1] The therapeutic and/or prophylactic agent according to [6] or [6-5] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, S891 or A883 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[6-6] The therapeutic and/or prophylactic agent according to [6] or [6-5] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, E768, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[6-7] The therapeutic and/or prophylactic agent according to [6] or [6-5] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F, V804M, V804L, S891A or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[6-7-1]The therapeutic and/or prophylactic agent according to [6], [6-5] or [6-7] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F or S891A in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[6-8] The therapeutic and/or prophylactic agent according to [6] or [6-6] above, wherein the point mutation is C634W, C634Y, E768D, V804M or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[0010]

[7] A therapeutic and/or prophylactic agent for a tumor used for a patient with a mutation in RET or for metastasis of the tumor, which comprises a compound represented by formula (I), a salt thereof or a solvate thereof as an active ingredient.

[8] The therapeutic and/or prophylactic agent according to [7] above, wherein the tumor is thyroid cancer or lung cancer.

[8-1] The therapeutic and/or prophylactic agent according to [7] or [8] above, wherein the patient is a patient confirmed to show activated RET tyrosine kinase in the tumor tissue.

[8-2] The therapeutic and/or prophylactic agent according to [7] or [8] above, wherein the patient is a patient with a mutation which induces activation of RET tyrosine kinase.

[8-2-1]The therapeutic and/or prophylactic agent according to any one of [7] to [8-2] above, wherein the patient is a patient with (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) a fusion gene of RET and/or a fusion protein of RET.

[8-2-2]The therapeutic and/or prophylactic agent according to any one of [7] to [8-2-1] above, wherein the patient is a patient with a fusion gene of RET and/or a fusion protein of RET.

[8-2-3]The therapeutic and/or prophylactic agent according to any one of [7] to [8-2] and [8-2-2] above, wherein the patient is a patient with KIF5B-RET, CCDC6-RET, NCOA4-RET or TRIM33-RET.

[8-3] The therapeutic and/or prophylactic agent according to any one of [7] to [8-2] above, wherein the patient is a patient with (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine

kinase, or (c) a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[9] The therapeutic and/or prophylactic agent according to [7] or [8] above, wherein the patient is a patient with a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[9-1] The therapeutic and/or prophylactic agent according to [8-3] or [9] above, wherein the another gene and protein are KIF5B, CCDC6, NCOA4 or TRIM33.

[9-2] The therapeutic and/or prophylactic agent according to [9] or [9-1] above, wherein the fusion gene and fusion protein comprises the tyrosine kinase domain of RET gene or protein and the coiled-coil domain of another gene or protein.

[9-2-1] The therapeutic and/or prophylactic agent according to any one of [9] to [9-2] above, wherein a polypeptide constituting the RET protein and a polynucleotide constituting the RET gene are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 3 or 4;
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the polypeptide shown in SEQ ID NO: 3 or 4; and
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 3 or 4.

[9-2-2] The therapeutic and/or prophylactic agent according to [9-1] above, wherein a polypeptide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 proteins and a polynucleotide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 genes are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

(1) the polypeptide constituting the KIF5B protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 30,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 30, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 30;

(2) the polypeptide constituting the CCDC6 protein is

(a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 31,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 31, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 31;

(3) the polypeptide constituting the NCOA4 protein is

(a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42; and

(4) the polypeptide constituting the TRIM33 protein is

(a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 45 or 46,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 45 or 46, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 45 or 46.

[9-2-3]The therapeutic and/or prophylactic agent according to [8-2-2] or [9] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

(a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

- (b) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (c) a polypeptide comprising an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;
- (e) a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 27 or 28, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28; and
- (f) a polypeptide comprising an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28.

[9-2-4]The therapeutic and/or prophylactic agent according to [8-2-2] or [9] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (b) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which carries activated tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;
- (c) a polypeptide which comprises an amino acid sequence with 90% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;
- (d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;

- (e) a polypeptide which comprises the amino acid sequence shown in SEQ ID NO: 27 or 28 and which carries activated RET tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity; and
- (f) a polypeptide which comprises an amino acid sequence with 90% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity.

[9-3] The therapeutic and/or prophylactic agent according to [9] or [9-2] above, wherein the fusion gene is any of (a) to (d) shown below:

- (a) a fusion gene which comprises a polynucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14;
- (b) a fusion gene consisting of a polynucleotide which hybridizes under stringent conditions to DNA consisting of a nucleotide sequence complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14 and which encodes a polypeptide having tyrosine kinase activity;
- (c) a fusion gene which comprises a polynucleotide encoding a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24; or
- (d) a fusion gene comprising a polynucleotide encoding a polypeptide which has substitution, deletion or insertion of one or more (e.g., several tens, 1 to 10, 1 to 5, 1 to 3) amino acids in a polypeptide having an amino acids sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity.

[0011]

[10] The therapeutic and/or prophylactic agent according to [7] or [8] above, wherein the patient is a patient with a point mutation in RET gene and/or protein.

[10-1] The therapeutic and/or prophylactic agent according to [10] above, wherein the point mutation in RET is a point mutation in the cysteine-rich domain or in the tyrosine kinase domain of RET tyrosine kinase.

[10-2] The therapeutic and/or prophylactic agent according to [10] or [10-1] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G,

2562A, 2600G, 2861T or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[10-2-1] The therapeutic and/or prophylactic agent according to any one of [10] to [10-2] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A or 2861T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[10-3] The therapeutic and/or prophylactic agent according to any one of [10] to [10-2], wherein the point mutation in RET is a mutation in the nucleotide 2091G, 2494G, 2600G or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[10-4] The therapeutic and/or prophylactic agent according to any one of [10] to [10-2] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T, 2600G>A, 2600G>C, 2861T>G or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[10-4-1] The therapeutic and/or prophylactic agent according to any one of [10] to [10-2] and [10-4] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T or 2861T>G in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[10-5] The therapeutic and/or prophylactic agent according to any one of [10] to [10-2], [10-4] above, wherein the point mutation in RET is 2091G>T, 2494G>C, 2600G>A or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[10-6] The therapeutic and/or prophylactic agent according to [10] or [10-1] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[10-6-1] The therapeutic and/or prophylactic agent according to [10], [10-1] or [10-6] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, S891 or A883 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[10-7] The therapeutic and/or prophylactic agent according to [10], [10-1] or [10-6] above, wherein the point mutation in RET is a mutation in the amino acid C609,

C611, C618, C620, C630, C634, E768, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[10-8] The therapeutic and/or prophylactic agent according to [10], [10-1] or [10-6] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F, V804M, V804L, S891A or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[10-8-1] The therapeutic and/or prophylactic agent according to [10], [10-1], [10-6] or [10-8] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F or S891A in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[10-9] The therapeutic and/or prophylactic agent according to any one of [10], [10-1] or [10-6] to [10-8] above, wherein the point mutation in RET is C634Y, E768D, V804M or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[10-10] The therapeutic and/or prophylactic agent according to any one of [10] to [10-9] above, wherein the patient is a patient detected for the presence of a mutation in RET by Sanger sequencing or FISH method.

[0012]

[11] The therapeutic and/or prophylactic agent according to any one of [1] to [10-10] above, wherein R¹ is ethyl.

[11-1] The therapeutic and/or prophylactic agent according to any one of [1] to [11] above, wherein the compound is a hydrochloride.

[11-2] The therapeutic and/or prophylactic agent according to any one of [1] to [11-1] above, wherein the therapeutic and/or prophylactic agent selectively inhibits RET.

[12] A RET inhibitor, which comprises a compound of formula (I), a salt thereof or a solvate thereof as an active ingredient.

[12-1] Use of a compound of formula (I), a salt thereof or a solvate thereof for inhibition of RET.

[12-2] A method for preventing and/or treating a tumor with a mutation in RET and metastasis of the tumor, which comprises administering a patient with an effective therapeutic amount of a compound represented by formula (I), a salt thereof or a solvate thereof.

[12-3] Use of a compound represented by formula (I), a salt thereof or a solvate thereof for prevention and/or treatment of a tumor with a mutation in RET and metastasis of the tumor.

[12-3-1] The use according to [12-3] above, wherein the mutation in RET is (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) the formation of a fusion gene of RET and/or a fusion protein of RET.

[12-3-2] The use according to [12-3] or [12-3-1] above, wherein the mutation in RET results in the formation of a fusion gene of RET and/or a fusion protein of RET.

[12-3-3] The use according to any one of [12] to [12-2-2] above, wherein the mutation in RET results in the formation of KIF5B-RET, CCDC6-RET, NCOA4-RET or TRIM33-RET.

[12-3-4] The use according to any one of [12-3] to [12-3-3] above, wherein the compound of formula (I), the salt thereof or the solvate thereof selectively inhibits RET.

[12-3-5] The use according to any one of [12-3] to [12-3-4] above, wherein R¹ is ethyl.

[12-3-6] The use according to any one of [12-3] to [12-3-5] above, wherein the compound is a hydrochloride.

[12-3-7] The use according to any one of [12-3] to [12-3-6] above, wherein the tumor is thyroid cancer or lung cancer.

[0013]

[13] A method for identifying a subject to be administered with a compound represented by formula (I), a salt thereof or a solvate thereof, which comprises the step of detecting a mutation in RET in a tissue from the subject.

[13-1] The method according to [13] above, wherein the tissue is a tissue confirmed to show activated RET tyrosine kinase.

[13-2] The method according to [13] above, wherein the tissue has a mutation which induces activation of RET tyrosine kinase.

[13-2-1] The method according to any one of [13] to [13-2] above, wherein the mutation in RET is (a) a mutation in the cysteine-rich domain of RET tyrosine

kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) the formation of a fusion gene of RET and/or a fusion protein of RET.

[13-2-2] The method according to any one of [13] to [13-2-1] above, wherein the mutation in RET results in the formation of a fusion gene of RET and/or a fusion protein of RET.

[13-2-3] The method according to any one of [13] to [13-2-2] above, wherein the mutation in RET results in the formation of KIF5B-RET, CCDC6-RET, NCOA4-RET or TRIM33-RET.

[13-3] The method according to any one of [13] to [13-2] above, wherein the tissue has (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[13-4] The method according to any one of [13] to [13-3] above, wherein the mutation in RET results in the formation of a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[13-5] The method according to [13-4] above, wherein another gene and protein are KIF5B, CCDC6, NCOA4 or TRIM33.

[13-6] The method according to [13-5] above, wherein the fusion gene and fusion protein comprise the tyrosine kinase domain of RET gene or protein and the coiled-coil domain of another gene or protein.

[13-6-1] The method according to any one of [13-4] to [13-6] above, wherein a polypeptide constituting the RET protein and a polynucleotide constituting the RET gene are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 3 or 4;
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the polypeptide shown in SEQ ID NO: 3 or 4; and
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 3 or 4.

[13-6-2] The method according to [13-5] above, wherein a polypeptide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 proteins and a polynucleotide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 genes are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

(1) the polypeptide constituting the KIF5B protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 30,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 30, or
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 30;

(2) the polypeptide constituting the CCDC6 protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 31,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 31, or
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 31;

(3) the polypeptide constituting the NCOA4 protein is

- (a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42,
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42, or
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42; and

(4) the polypeptide constituting the TRIM33 protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 45 or 46,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 45 or 46, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 45 or 46.

[13-6-3] The method according to [13-2-1], [13-2-2], [13-3] or [13-4] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

(a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(b) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(c) a polypeptide comprising an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;

(e) a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 27 or 28, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28; and

(f) a polypeptide comprising an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28.

[13-6-4] The method according to [13-2-1], [13-2-2], [13-3], [13-4] or [13-6-3] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

(a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

- (b) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which carries activated tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;
- (c) a polypeptide which comprises an amino acid sequence with 90% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;
- (d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;
- (e) a polypeptide which comprises the amino acid sequence shown in SEQ ID NO: 27 or 28 and which carries activated RET tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity; and
- (f) a polypeptide which comprises an amino acid sequence with 90% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity.

[13-7] The method according to [13-6] above, wherein the fusion gene is any of (a) to (d) shown below:

- (a) a fusion gene which comprises a polynucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14;
- (b) a fusion gene consisting of a polynucleotide which hybridizes under stringent conditions to DNA consisting of a nucleotide sequence complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14 and which encodes a polypeptide having tyrosine kinase activity;
- (c) a fusion gene which comprises a polynucleotide encoding a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24; or
- (d) a fusion gene comprising a polynucleotide encoding a polypeptide which has substitution, deletion or insertion of one or more (e.g., several tens, 1 to 10, 1 to 5, 1

to 3) amino acids in a polypeptide having an amino acids sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity.

[13-8] The method according to [13] to [13-2] above, wherein the tissue has a point mutation in RET.

[13-9] The method according to [13-8] above, wherein the tissue has a point mutation in the cysteine-rich domain or in the tyrosine kinase domain of RET tyrosine kinase.

[0014]

[13-10] The method according to [13-8] or [13-9] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A, 2600G, 2861T or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[13-10-1] The method according to any one of [13-8] to [13-10] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A or 2861T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[13-11] The method according to any one of [13-8] to [13-10] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2494G, 2600G or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[13-12] The method according to any one of [13-8] to [13-10] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T, 2600G>A, 2600G>C, 2861T>G or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[13-12-1] The method according to any one of [13-8] to [13-10] and [13-12] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T or 2861T>G in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[13-13] The method according to any one of [13-8] to [13-12] above, wherein the point mutation is 2091G>T, 2494G>C, 2600G>A or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[13-14] The method according to [13-8] or [13-9] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634,

G691, E768, Y791, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[13-14-1] The method according to [13-8], [13-9] or [13-14] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, S891 or A883 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[13-15] The method according to [13-8], [13-9] or [13-14] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, E768, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[13-16] The method according to [13-8], [13-9] or [13-14] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F, V804M, V804L, S891A or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[13-16-1] The method according to [13-8], [13-9] or [13-14] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F or S891A in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[13-17] The method according to any one of [13-8] to [13-16] above, wherein the point mutation in RET is C634Y, E768D, V804M or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[13-18] The method according to any one of [13] to [13-17] above, wherein the method identifies a subject to be administered with a compound represented by formula (I), a salt thereof or a solvate thereof for treatment and/or prevention of a tumor with a mutation in RET or metastasis of the tumor.

[13-19] The method according to any one of [13] to [13-18] above, wherein the tumor is thyroid cancer or lung cancer.

[13-20] The method according to any one of [13] to [13-19] above, wherein the compound represented by formula (I), the salt thereof or the solvate thereof selectively inhibits RET.

[13-21] The method according to any one of [13] to [13-20] above, wherein R¹ is ethyl.

[13-22] The method according to any one of [13] to [13-21] above, wherein the compound of formula (I), the salt thereof or the solvate thereof is hydrochloride of the compound of formula (I).

[0015]

[14] A prophylactic and/or therapeutic method for a tumor with a mutation in RET and for metastasis of the tumor, which comprises identifying a patient with a mutation in RET and administering the patient with an effective therapeutic amount of a compound represented by formula (I), a salt thereof or a solvate thereof.

[15] A method for identifying or preliminarily identifying a patient sensitive to a compound represented by formula (I), a salt thereof or a solvate thereof, which comprises the steps of:

detecting the presence of a mutation in RET in a sample obtained from the patient;
and

determining or preliminarily determining that the patient has sensitivity to the compound, the salt thereof or the solvate thereof, on the basis of the presence of a mutation in RET in the sample.

[15-1] The method according to [15] above, further comprising the step of detecting activation of RET tyrosine kinase.

[15-2] The method according to [15] above, wherein the mutation in RET is a mutation which induces activation of RET tyrosine kinase.

[15-2-1] The method according to any one of [15] to [15-2] above, wherein the mutation in RET is (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) the formation of a fusion gene of RET and/or a fusion protein of RET.

[15-2-2] The method according to any one of [15] to [15-2-1] above, wherein the mutation in RET results in the formation of a fusion gene of RET and/or a fusion protein of RET.

[15-2-3] The method according to any one of [15] to [15-2-2] above, wherein the mutation in RET results in the formation of KIF5B-RET, CCDC6-RET, NCOA4-RET or TRIM33-RET.

[15-3] The method according to any one of [15] to [15-2] above, wherein the mutation in RET is (a) a mutation in the cysteine-rich domain of RET tyrosine kinase,

(b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) the formation of a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[15-4] The method according to any one of [15] to [15-3] above, wherein the mutation in RET results in the formation of a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

[15-5] The method according to [15-4] above, wherein the other gene and protein are KIF5B, CCDC6, NCOA4 or TRIM33.

[15-6] The method according to [15-4] or [15-5] above, wherein the fusion gene between RET gene and another gene and the fusion protein between RET protein and another protein comprise the tyrosine kinase domain of RET gene or protein and the coiled-coil domain of another gene or protein.

[15-6-1] The method according to any one of [15-4] to [15-6] above, wherein a polypeptide constituting the RET protein and a polynucleotide constituting the RET gene are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 3 or 4;
- (b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the polypeptide shown in SEQ ID NO: 3 or 4; and
- (c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 3 or 4.

[15-6-2] The method according to [15-5] above, wherein a polypeptide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 proteins and a polynucleotide constituting each of the KIF5B, CCDC6, NCOA4 and TRIM33 genes are any of the following polypeptides and any of polynucleotides encoding the polypeptides:

(1) the polypeptide constituting the KIF5B protein is

- (a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 30,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 30, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 30;

(2) the polypeptide constituting the CCDC6 protein is

(a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 31,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 31, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 31;

(3) the polypeptide constituting the NCOA4 protein is

(a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42; and

(4) the polypeptide constituting the TRIM33 protein is

(a) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 45 or 46,

(b) a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 45 or 46, or

(c) a polypeptide consisting of an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 45 or 46.

[15-6-3] The method according to [15-2-1], [15-2-2], [15-3] or [15-4] above, wherein a polypeptide constituting the fusion protein and a polynucleotide

constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (b) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (c) a polypeptide comprising an amino acid sequence with 80% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;
- (e) a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 27 or 28, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28; and
- (f) a polypeptide comprising an amino acid sequence with 80% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28.

[15-6-4] The method according to [15-2-1], [15-2-2], [15-3] or [15-4] above, wherein a polypeptide constituting the fusion protein and a polynucleotide constituting the fusion gene are any of the following polypeptides (a) to (f) and any of polynucleotides encoding the polypeptides:

- (a) a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;
- (b) a polypeptide which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which carries activated tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;

- (c) a polypeptide which comprises an amino acid sequence with 90% or higher identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity;
- (d) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 27 or 28;
- (e) a polypeptide which comprises the amino acid sequence shown in SEQ ID NO: 27 or 28 and which carries activated RET tyrosine kinase, or a polypeptide which comprises an amino acid sequence with substitution, deletion or insertion of 1 to 10 amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity; and
- (f) a polypeptide which comprises an amino acid sequence with 90% or higher identity to the amino acid sequence shown in SEQ ID NO: 27 or 28 and which has tyrosine kinase activity.

[15-6-5] The method according to [15-3] or [15-4] above, wherein the fusion gene is any of (a) to (d) shown below:

- (a) a fusion gene which comprises a polynucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14;
- (b) a fusion gene consisting of a polynucleotide which hybridizes under stringent conditions to DNA consisting of a nucleotide sequence complementary to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14 and which encodes a polypeptide having tyrosine kinase activity;
- (c) a fusion gene which comprises a polynucleotide encoding a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24; or
- (d) a fusion gene comprising a polynucleotide encoding a polypeptide which has substitution, deletion or insertion of one or more (e.g., several tens, 1 to 10, 1 to 5, 1 to 3) amino acids in a polypeptide having an amino acids sequence selected from the group consisting of SEQ ID NOs: 15 to 24 and which has tyrosine kinase activity.

[15-7] The method according to any one of [15] to [15-2] above, wherein the mutation in RET is a point mutation.

[15-8] The method according to [15-7] above, wherein the point mutation is a point mutation in the cysteine-rich domain or in the tyrosine kinase domain of RET tyrosine kinase.

[15-9] The method according to [15-7] or [15-8] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A, 2600G, 2861T or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[15-9-1] The method according to any one of [15-7] to [15-9] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A or 2861T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[15-10] The method according to any one of [15-7] or [15-9] above, wherein the point mutation is a mutation in the nucleotide 2091G, 2494G, 2600G or 2943T of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[15-11] The method according to any one of [15-7] to [15-9] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T, 2600G>A, 2600G>C, 2861T>G or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[15-11-1] The method according to any one of [15-7] to [15-9-1] and [15-11] above, wherein the point mutation is 2091G>T, 2261G>A, 2494G>C, 2562A>T or 2861T>G in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[15-12] The method according to any one of [15-7] to [15-11] above, wherein the point mutation is 2091G>T, 2494G>C, 2600G>A or 2943T>C in a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1.

[15-13] The method according to [15-7] or [15-8] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[15-13-1] The method according to [15-7], [15-8] or [15-13] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, S891 or A883 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[15-14] The method according to [15-7], [15-8] or [15-13] above, wherein the point mutation is a mutation in the amino acid C609, C611, C618, C620, C630, C634, E768, V804, S891, A883 or M918 of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[15-15] The method according to [15-7], [15-8] or [15-13] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F, V804M, V804L, S891A or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[15-15-1] The method according to [15-7], [15-8], [15-13] or [15-15] above, wherein the point mutation is C634W, C634Y, G691S, E768D, Y791F or S891A in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[15-16] The method according to any one of [15-7] to [15-15], wherein the point mutation is C634W, C634Y, E768D, V804M or M918T in a polypeptide having the amino acid sequence shown in SEQ ID NO: 3.

[15-17] The method according to any one of [15] to [15-16] above, wherein the patient is a patient with thyroid cancer or lung cancer.

[15-18] The method according to any one of [15] to [15-17] above, wherein the patient is a patient with thyroid medullary cancer or non-small cell lung cancer.

[15-19] The method according to any one of [15] to [15-18] above, wherein the compound of formula (I), the salt thereof or the solvate thereof selectively inhibits RET.

[15-20] The method according to any one of [15] to [15-18] above, wherein R¹ is ethyl.

[15-21] The method according to any one of [15] to [15-19] above, wherein the compound is a hydrochloride.

[16] A method for predicting the sensitivity of a patient to a compound of formula (I), a salt thereof or a solvate thereof, which comprises the steps of;

(1) confirming the presence or absence of a mutation in RET in a sample obtained from the patient; and

(2) determining or preliminarily determining that the patient has sensitivity to the compound of formula (I), the salt thereof or the solvate thereof, provided that the mutation in RET is present.

EFFECTS OF THE INVENTION

[0016]

The therapeutic and/or prophylactic agent of the present invention has a potent inhibitory effect against RET, particularly against RET tyrosine kinase, and is useful as a prophylactic or therapeutic agent (particularly therapeutic agent) for proliferative diseases. Moreover, the active ingredient in the present invention is useful as a prophylactic or therapeutic agent (particularly therapeutic agent) for diseases including various types of cancers, such as leukemia (e.g., acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia), malignant lymphoma (e.g., Hodgkin's lymphoma, non-Hodgkin's lymphoma), brain tumor, neuroblastoma, glioma, thyroid cancer, myelodysplastic syndrome, head and neck cancer, esophageal cancer, gastric cancer, colorectal cancer, breast cancer, ovarian cancer, lung cancer, pancreatic cancer, liver cancer, gallbladder cancer, skin cancer, malignant melanoma, kidney cancer, renal pelvic and ureteral cancer, bladder cancer, uterine cancer, testicular cancer and prostate cancer. The active ingredient in the present invention is further useful as a prophylactic or therapeutic agent (particularly therapeutic agent) for infiltration and metastasis of solid cancers.

The present invention achieves the identification of a cancer or a patient with a mutation in RET and achieves the effective treatment, etc. of such a patient using the compound represented by formula (I) or the like.

BRIEF DESCRIPTION OF THE DRAWING

[0017]

FIG. 1 shows the antitumor activity of compound 1 using xenograft mouse models having CCDC6-RET fusion gene (Example 6).

Mode for Carrying out the Invention

[0018]

An explanation will be given below of the therapeutic or prophylactic agent of the present invention and preparation procedures thereof.

Definitions

In the context of the present invention, the term "C₁₋₆ alkyl group" refers to a monovalent group derived from a linear or branched aliphatic hydrocarbon containing 1 to 6 carbon atoms by removing any one of the hydrogen atoms. More specifically, examples include a methyl group, an ethyl group, an isopropyl group, a butyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a t-butyl group, a pentyl group, an isopentyl group, a 2,3-dimethylpropyl group, a hexyl group, a 2,3-dimethylhexyl group, a 1,1-dimethylpentyl group, a heptyl group and an octyl group. Preferred is a C₁₋₆ alkyl group, more preferred is a C₁₋₅ alkyl group, even more preferred is a C₁₋₄ alkyl group, and still even more preferred is a C₁₋₃ alkyl group.

[0019]

In the context of the present invention, the expression "with a mutation in RET", "a mutation in RET" or "a mutation of RET" is intended to mean that a mutation occurs in RET gene and/or RET protein. In the context of the present invention, the expression "with a mutation in RET", "a mutation in RET" includes a point mutation, a deletion mutation or an insertion mutation in RET gene and/or RET protein, translocation- or inversion-mediated fusion between RET gene and another gene, as well as fusion protein formation between RET protein and another protein. The expression "with a mutation in RET", "a mutation in RET" or "a mutation of RET" further includes amplification of RET gene and/or amplification of RET protein, caused by an increased number of DNA regions on the genome compared to the normal state upon cleavage and rejoining of RET gene, impairment in the repair functions for RET gene, etc.

In the context of the present invention, the term "RET gene" is intended to mean a gene encoding RET (rearranged during transfection) tyrosine kinase. The RET gene of the present invention is intended to mean RET gene of any origin. Specifically, examples include, but are not limited to, a gene having a polynucleotide consisting of the nucleotide sequence shown in SEQ ID NO: 1 or 2, and a polynucleotide encoding a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 3 or 4.

[0020]

In the context of the present invention, the term "RET protein" is intended to mean a protein consisting of an amino acid sequence constituting RET tyrosine kinase. The RET protein of the present invention is intended to mean RET protein of any origin. Specifically, examples include, but are not limited to, a protein having a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 3 or 4. It is known that there are three types of proteins RET9, RET43 and RET51 for RET tyrosine kinase due to differences in carboxyl-terminal splicing (TRENDS in Genetics, 2006, vol. 22, p. 627-636), and polypeptides consisting of amino acids constituting these three types of proteins also fall within "RET protein."

[0021]

In the present invention, the polypeptide constituting the RET protein and the polynucleotide constituting the RET gene include the following polypeptides and genes encoding the polypeptides:

a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10, particularly preferably 1 to 5) amino acids in the polypeptide shown in SEQ ID NO: 3 or 4; and

a polypeptide consisting of an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to the amino acid sequence shown in SEQ ID NO: 3 or 4.

In the context of the present invention, the expression "polynucleotide encoding a polypeptide" encompasses every polynucleotide capable of encoding a specific polypeptide and encompasses any of genomic DNA and cDNA. The polynucleotide includes even a degenerate polynucleotide composed of any codon encoding the same amino acid.

[0022]

In the present invention, the identity of an amino acid sequence can be calculated by: properly aligning at least two sequences to be compared with each other; determining identical amino acid residues between the sequences; determining the number of matching sites; and subsequently dividing the number of the matching sites by the total number of residues in the sequence region to be compared and multiplying the obtained numeric value by 100. For example, the identity of a specific amino acid sequence to the amino acid sequence shown in SEQ ID NO: 3

can be calculated by: determining the number of matching sites between two sequences, i.e., the amino acid sequence shown in SEQ ID NO: 3 and the specific amino acid sequence, by the above method; and subsequently dividing the number of the matching sites by the total number of residues in the amino acid sequence shown in SEQ ID NO: 3 and multiplying the obtained numeric value by 100.

[0023]

Alternatively, the identity of an amino acid sequence may be determined by the Karlin-Altschul BLAST algorithm (Proc. Natl. Acad. Sci. USA (1993) 90: 5873-7). On the basis of this algorithm, a program called BLASTN or BLASTX has been developed (Altschul et al., J. Mol. Biol. (1990) 215: 403-10). Each nucleotide sequence can be analyzed by BLASTN on the basis of BLAST using parameters set to, for example, score = 100 and wordlength = 12. Also, each amino acid sequence can be analyzed by BLASTX on the basis of BLAST using parameters set to, for example, score = 50 and wordlength = 3. In the case of using BLAST and Gapped BLAST programs, the default parameters of each program are used. Specific approaches of these analysis methods are known in the art (see information provided by the website of BLAST (Basic Local Alignment Search Tool), NCBI (National Center for Biotechnology Information)).

[0024]

In the context of the present invention, the term "hybridizing" is intended to mean hybridizing to a target DNA or polynucleotide under stringent conditions. The stringent conditions can be determined on the basis of the melting temperature (T_m) of a nucleic acid to form a complex according to a routine method. Specifically, the stringent conditions involve "5 × SSPE, 5 × Denhardt's solution, 0.5% SDS, 50% formamide, 200 µg/ml salmon sperm DNA, 42°C overnight" as conditions for hybridization and "0.5 × SSC, 0.1% SDS, 42°C" as conditions for washing. More stringent conditions involve "5 × SSPE, 5 × Denhardt's solution, 0.5% SDS, 50% formamide, 200 µg/ml salmon sperm DNA, 42°C overnight" as conditions for hybridization and "0.2 × SSC, 0.1% SDS, 65°C" as conditions for washing.

[0025]

The expression "with a mutation in RET", "a mutation in RET" or "a mutation of RET" further includes a state where a mutation which induces activation of RET tyrosine kinase or a mutation which activates RET tyrosine kinase and induces oncogenesis (e.g., thyroid cancer, lung cancer) has occurred in RET gene and/or RET protein. The activation of RET tyrosine kinase can be confirmed by detecting phosphorylated RET in a tumor tissue by immunostaining or the like using an anti-phosphorylated RET antibody.

In the context of the present invention, the expression "activation of RET tyrosine kinase" or "state where RET tyrosine kinase has been activated" is intended to mean that an amino acid residue (e.g., a tyrosine residue) contained in RET tyrosine kinase has been phosphorylated, and includes the amount of phosphorylated RET tyrosine kinase protein is increased in a subject (e.g., a sample taken from a subject) (e.g., when compared to a normal subject). In addition, the expression "activation of RET tyrosine kinase" or "state where RET tyrosine kinase has been activated" includes a state where phosphorylated RET tyrosine kinase induces phosphorylation of a protein serving as a target of RET tyrosine kinase (hereinafter referred to as a target protein). The expression "activation of RET tyrosine kinase" or "state where RET tyrosine kinase has been activated" include not only the amount of phosphorylated RET tyrosine kinase protein, but also the amount of the above target protein in a phosphorylated form is increased.

In the context of the present invention, the expression "having tyrosine kinase activity" is intended to mean having activity as an enzyme that phosphorylates an amino acid residue, for example, a tyrosine residue, contained in tyrosine kinase. The tyrosine kinase activity of a polypeptide constituting the RET protein can be confirmed by, for example, the above method. In addition, the expression "having tyrosine kinase activity" includes having activity as an enzyme that phosphorylates an amino acid residue of a targeted protein.

[0026]

Mutations reported to induce activation of RET tyrosine kinase include (1) a mutation in the cysteine-rich domain of RET, (2) a mutation in the tyrosine kinase domain of RET, and (3) formation of a fusion gene between RET gene and another gene or a fusion protein between RET protein and another protein (TRENDS in

Genetics, 2006, vol. 22, p. 627-636). The human RET gene is located on chromosome 10 (10q11.2) and composed of 21 exons. The "cysteine-rich domain of RET" refers to a region rich in cysteine found in RET tyrosine kinase, and a polynucleotide encoding this domain is located at exons 10 and 11. The "tyrosine kinase domain of RET" refers to a region having tyrosine kinase activity found in RET tyrosine kinase, and a polynucleotide encoding this domain is located at exons 12 to 18 (TRENDS in Genetics, 2006, vol. 22, p. 627-636).

[0027]

Specific examples of the above mutations (1) to (3) include those listed below. In the context of the present invention, the expression "with a mutation in RET" or "a mutation in RET" includes a state where any of these mutations (1) to (3) has occurred in RET gene and/or RET protein.

(1) Mutation in the cysteine-rich domain

A mutation in C609, C611, C618, C620, C630, C634 or elsewhere in the amino acid sequence shown in SEQ ID NO: 3 (e.g., C634W, C634Y)

(2) Mutation in the tyrosine kinase domain

A mutation in E768, V804, S891, A883, M918 or elsewhere in the amino acid sequence shown in SEQ ID NO: 3 (e.g., E768D, V804M, V804L, M918T)

(3) Formation of a fusion gene between RET gene and another gene or a fusion protein between RET protein and another protein

Formation of KIF5B-RET fusion gene and/or fusion protein comprising the coiled-coil domain of KIF5B and the tyrosine kinase domain of RET

Formation of CCDC6-RET fusion gene and/or fusion protein comprising the coiled-coil domain of CCDC6 and the tyrosine kinase domain of RET

Formation of NCOA4-RET fusion gene and/or fusion protein comprising the coiled-coil domain of NCOA4 and the tyrosine kinase domain of RET

Formation of TRIM33-RET fusion gene and/or fusion protein comprising the coiled-coil domain of TRIM33 and the tyrosine kinase domain of RET

[0028]

In the context of the present invention, the expression "gene of KIF5B" or "KIF5B gene" is intended to mean a gene encoding KIF5B (Kinesin family protein 5B), and the expression "protein of KIF5B" or "KIF5B protein" is intended to mean a

protein consisting of an amino acid sequence constituting KIF5B. These terms are intended to mean a gene or a protein of KIF5B of any origin. Examples of a polynucleotide constituting the KIF5B gene and a polypeptide constituting the KIF5B protein specifically include, but are not limited to, a polynucleotide consisting of the nucleotide sequence shown in SEQ ID NO: 29 and a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 30. The polypeptide constituting the KIF5B protein and the polynucleotide constituting the KIF5B gene further include the following polypeptides and polynucleotides encoding the polypeptides:

a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10, particularly preferably 1 to 5) amino acids in the amino acid sequence shown in SEQ ID NO: 30; and

a polypeptide consisting of an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to the amino acid sequence shown in SEQ ID NO: 30.

[0029]

The human KIF5B gene is located in chromosome 10 and composed of 26 exons. Candidates for the nucleotide sequence of KIF5B-RET fusion gene include, but are not limited to, those shown in SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13 and SEQ ID NO: 14. Candidates for the amino acid sequence of KIF5B-RET fusion protein include, but are not limited to, those shown in SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23 and SEQ ID NO: 24. Such KIF5B-RET fusion gene and fusion protein are reported to comprise the coiled-coil domain of KIF5B and the kinase domain of RET (Nature Medicine. 2012, 18, p. 378-381, Nature Medicine. 2012, 18, p. 382-384). In the present invention, the polypeptide constituting the KIF5B-RET fusion protein and the polynucleotide constituting the KIF5B-RET fusion gene additionally include the following polypeptides and polynucleotides encoding the polypeptides:

(i) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10,

particularly preferably 1 to 5) amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24;

(ii) a polypeptide comprising an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 15 to 24; and

(iii) a polypeptide which is the polypeptide (i) or (ii) and which has tyrosine kinase activity.

[0030]

In the context of the present invention, the expression "gene of CCDC6" or "CCDC6 gene" is intended to mean a gene encoding CCDC6 (coiled-coil domain containing 6), and the expression "protein of CCDC6" or "CCDC6 protein" is intended to mean a protein consisting of an amino acid sequence constituting CCDC6. These terms are intended to mean a gene or a protein of CCDC6 of any origin. Examples of a polynucleotide constituting the CCDC6 gene and a polypeptide constituting the CCDC6 protein specifically include, but are not limited to, a polynucleotide consisting of the nucleotide sequence shown in SEQ ID NO: 31 and a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 32. The polypeptide constituting the CCDC6 protein and the polynucleotide constituting the CCDC6 gene further include the following polypeptides and polynucleotides encoding the polypeptides:

a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10, particularly preferably 1 to 5) amino acids in the amino acid sequence shown in SEQ ID NO: 31; and

a polypeptide consisting of an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to the amino acid sequence shown in SEQ ID NO: 31.

Human CCDC6 is located in chromosome 10 and composed of 9 exons.

Examples of the nucleotide sequence of CCDC6-RET fusion gene include, but are not limited to, those shown in SEQ ID NOs: 25 and 26. Examples of the amino acid sequence of the CCDC6-RET fusion protein include, but are not limited to, those shown in SEQ ID NOs: 27 and 28. Such CCDC6-RET fusion gene and

fusion protein are reported to comprise the coiled-coil domain of CCDC6 and the tyrosine kinase domain of RET (Nat Med. 2012 Feb 12; 18 (3): 378-81).

Examples of the polypeptide constituting the CCDC6-RET fusion protein and the polynucleotide constituting the CCDC6-RET fusion gene additionally include the following polypeptides and polynucleotides encoding the polypeptides:

- (i) a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 27 or 28, or a polypeptide comprising an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10, particularly preferably 1 to 5) amino acids in the amino acid sequence shown in SEQ ID NO: 27 or 28;
- (ii) a polypeptide comprising an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to the amino acid sequence shown in SEQ ID NO: 27 or 28; and
- (iii) a polypeptide which is the polypeptide (i) or (ii) and which has tyrosine kinase activity.

[0031]

In the context of the present invention, the expression "gene of NCOA4" or "NCOA4 gene" is intended to mean a gene encoding NCOA4 (nuclear receptor coactivator 4), and the expression "protein of NCOA4" or "NCOA4 protein" is intended to mean a protein consisting of an amino acid sequence constituting NCOA4. These terms are intended to mean a gene or a protein of NCOA4 of any origin. Examples of a polynucleotide constituting the NCOA4 gene and a polypeptide constituting the NCOA4 protein specifically include, but are not limited to, a polynucleotide consisting of a nucleotide sequence selected from the group consisting of SEQ ID NOs: 33 to 37 and a polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42. The polypeptide constituting the NCOA4 protein and the polynucleotide constituting the NCOA4 gene further include the following polypeptides and polynucleotides encoding the polypeptides:

a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10, particularly preferably 1 to 5) amino acids in an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42; and

a polypeptide consisting of an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 38 to 42.

Human NCOA4 is located in chromosome 10. A gene in which NCOA4 exon 6 is fused with RET exon 12 is reported as a NCOA4-RET fusion gene. This fusion gene and its fusion protein are reported to comprise the coiled-coil domain of NCOA4 and the tyrosine kinase domain of RET (J Clin Oncol, 30 (35), Dec 10, 2012, p. 4352-9).

[0032]

In the context of the present invention, the expression "gene of TRIM33" or "TRIM33 gene" is intended to mean a gene encoding TRIM33 (tripartite motif-containing 33), and the expression "protein of TRIM33" or "TRIM33 protein" is intended to mean a protein consisting of an amino acid sequence constituting TRIM33. These terms are intended to mean a gene or a protein of TRIM33 of any origin. Examples of a polynucleotide constituting the TRIM33 gene and a polypeptide constituting the TRIM33 protein specifically include, but are not limited to, a polynucleotide consisting of the nucleotide sequence shown in SEQ ID NO: 43 or 44 and a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 45 or 46. The polypeptide constituting the TRIM33 protein and the polynucleotide constituting the TRIM33 gene further include the following polypeptides and polynucleotides encoding the polypeptides:

a polypeptide consisting of an amino acid sequence with substitution, deletion or insertion of one or more (preferably 1 to 10, particularly preferably 1 to 5) amino acids in the amino acid sequence shown in SEQ ID NO: 45 or 46; and

a polypeptide consisting of an amino acid sequence with 80% or higher (preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher) identity to the amino acid sequence shown in SEQ ID NO: 45 or 46.

[0033]

Human TRIM33 is located in chromosome 1. A gene in which TRIM33 exon 14 is fused with RET exon 12 is reported as a TRIM33-RET fusion gene. This fusion gene and its fusion protein are reported to comprise the coiled-coil

domain of TRIM33 and the tyrosine kinase domain of RET (Cancer Discov, 3 (6), Jun 2013, p. 630-5).

The coiled-coil domain is a domain involved in protein dimerization. KIF5B-RET, CCDC6-RET, NCOA4-RET and TRIM33-RET are therefore considered to form dimers through their coiled-coil domains. These proteins are considered to cause the abnormal activation of RET tyrosine kinase via the dimerization between their coiled-coil domains to induce oncogenesis (Nature Medicine. 2012, 18, p. 378-381; Nature Medicine. 2012, 18, p. 382-384; J Clin Oncol, 30 (35), Dec 10, 2012, p. 4352-9; and Cancer Discov 2013 Jun, 3 (6), Jun 2013, p. 630-5).

[0034]

Examples of a mutation in RET protein in thyroid cancer (e.g., thyroid medullary cancer) include C634W, C634Y, E768D, V804M, V804L and M918T mutations in the amino acid sequence shown in SEQ ID NO: 3 (the amino acid sequence of RET). The expressions "C634W," "C634Y," "E768D," "V804M," "V804L" and "M918T" each represent an amino acid mutation, expressed with a numeral representing a specific position which is sandwiched between single-letter symbols of amino acids before and after the mutation. For example, "C634W" denotes a Cys to Trp substitution in the 634th amino acid from the N-terminus of a specific amino acid sequence. Namely, the numeral represents the amino acid position counted from the N-terminus of a specific amino acid sequence, while the single-letter symbols of amino acids appearing before and after the numeral represent amino acids before and after the substitution, respectively.

[0035]

Mutations in RET gene corresponding to the above mutations include 2091G>T, 2494G>C, 2600G>A, 2600G>C and 2943T>C mutations in the nucleotide sequence shown in SEQ ID NO: 1 (the nucleotide sequence of RET). The expressions "2091G>T," "2494G>C," "2600G>A," "2600G>C" and "2943T>C" each represent a nucleotide mutation, expressed with a numeral representing a specific position followed by bases before and after the mutation. For example, "2091G>T" denotes a G to T substitution in the 2091st nucleotide from the 5' end of a specific base sequence. Namely, the numeral represents the base position counted from the

5' end of a specific base sequence, while the base appearing after the numeral and before the symbol ">" represents a base before the substitution and the base appearing after the symbol ">" represents a base after the substitution.

Examples of a mutation in RET in lung cancer (e.g., non-small cell lung cancer) include the formation of KIF5B-RET fusion gene and/or protein, CCDC6-RET fusion gene and/or protein, NCOA4-RET fusion gene and/or protein, TRIM33-RET fusion gene and/or protein, etc. More specifically, examples include, but are not limited to, those listed below.

Formation of KIF5B-RET fusion gene and/or fusion protein comprising the coiled-coil domain of KIF5B and the tyrosine kinase domain of RET

Formation of CCDC6-RET fusion gene and/or fusion protein comprising the coiled-coil domain of CCDC6 and the tyrosine kinase domain of RET

Formation of NCOA4-RET fusion gene and/or fusion protein comprising the coiled-coil domain of NCOA4 and the tyrosine kinase domain of RET

Formation of TRIM33-RET fusion gene and/or fusion protein comprising the coiled-coil domain of TRIM33 and the tyrosine kinase domain of RET

[0036]

In the context of the present invention, the expression "fusion gene of RET," "fusion gene between RET gene and another gene" refers to a gene in which all or a part of RET gene is fused with all or a part of another gene (e.g., KIF5B gene, CCDC6 gene, NCOA4 gene).

In the context of the present invention, the term "KIF5B-RET fusion gene" refers to a gene in which all or a part of RET gene is fused with all or a part of KIF5B gene. The term "CCDC6-RET fusion gene" refers to a gene in which all or a part of RET gene is fused with all or a part of CCDC6 gene. The term "NCOA4-RET fusion gene" refers to a gene in which all or a part of RET gene is fused with all or a part of NCOA4 gene. The term "TRIM33-RET fusion gene" refers to a gene in which all or a part of RET gene is fused with all or a part of TRIM33 gene.

In the context of the present invention, the expression "fusion protein of RET," "fusion protein between RET protein and another protein" refers to a protein in which all or a part of RET protein is fused with all or a part of another protein (e.g., KIF5B protein, CCDC6 protein, NCOA4 protein, TRIM33 protein).

[0037]

In the context of the present invention, the term "KIF5B-RET fusion protein" refers to a protein in which all or a part of RET protein is fused with all or a part of KIF5B protein. The term "CCDC6-RET fusion protein" refers to a protein in which all or a part of RET protein is fused with all or a part of CCDC6 protein. The term "NCOA4-RET fusion protein" refers to a protein in which all or a part of RET protein is fused with all or a part of NCOA4 protein. The term "TRIM33-RET fusion protein" refers to a protein in which all or a part of RET protein is fused with all or a part of TRIM33 protein.

In the context of the present invention, the term "KIF5B-RET" is intended to mean KIF5B-RET fusion gene and/or KIF5B-RET fusion protein. The term "CCDC6-RET" is intended to mean CCDC6-RET fusion gene and/or CCDC6-RET fusion protein. The term "NCOA4-RET" is intended to mean NCOA4-RET fusion gene and/or NCOA4-RET fusion protein. The term "TRIM33-RET" is intended to mean TRIM33-RET fusion gene and/or TRIM33-RET fusion protein.

The expression "tumor with a mutation in RET" is intended to mean a tumor with a mutation in RET gene and/or protein in tumor cells.

[0038]

The term "therapeutic agent" is intended to mean a pharmaceutical agent for directly or indirectly ameliorating a target disease or for preventing exacerbations of the target disease. More specifically, it is intended to mean a pharmaceutical agent for use in growth inhibition or size reduction of tumor tissues, inhibition of metastasis, reduction of tumor markers, amelioration of systemic symptoms or extension of survival period in a patient, etc.

The term "prophylactic agent" is intended to mean a pharmaceutical agent for use in pre-treatment of a patient at risk of suffering from a target disease such that the target disease is not developed.

The expression "metastasis of the tumor" is intended to mean metastasis of the primary tumor to other tissues. A therapeutic agent for "metastasis of the tumor" is intended to mean a pharmaceutical agent for inhibiting or suppressing metastasis of the tumor, or a pharmaceutical agent for growth inhibition or size reduction of tumor recurring as a result of metastasis. A prophylactic agent for

"metastasis of the tumor" is intended to mean a pharmaceutical agent for use in pre-treatment such that the tumor does not metastasize or does not recur as a result of metastasis.

[0039]

The expression "tumors metastasized from tumors" is intended to mean that the tumors listed as primary tumors metastasize to other tissues and develop therein.

The expression "subject to be administered" is intended to mean a subject for which a pharmaceutical agent can be expected to provide a therapeutic effect based on its mechanism of action. More specifically, it is intended to mean a patient with a proliferative disease for which growth inhibition or size reduction of tumor tissues, inhibition of metastasis, reduction of tumor markers, and amelioration of systemic symptoms in the patient can be expected.

The expression "tissue from the subject" is intended to mean a tissue contained in blood, alveoli, a biopsy sample, a sputum sample or the like taken from a subject such as a patient.

The expression "patient with a mutation in RET" is intended to mean that the patient has a mutation in RET gene and/or protein either in tumor or non-tumor tissue taken from a patient.

[0040]

The term "RET inhibitor" is intended to mean a pharmaceutical agent which inhibits the activity of RET kinase, preferably a pharmaceutical agent which binds to RET kinase and has an inhibitory effect against the activity of RET kinase.

The expression "selectively inhibiting RET" is intended to mean that inhibitory activity against RET tyrosine kinase is high in terms of IC₅₀ value when compared with inhibitory activity against many other kinases (e.g., ABL, EGFR, FGFR2, HER2, IGF1R, JAK1, KIT, MET, AKT1, MEK1) except for ALK.

The expression "preliminarily determining" or "preliminarily identifying" is intended to mean providing information about the presence of a mutation in RET in order to determine or identify a sensitive patient.

[0041]

In the present invention, the salt of the compound represented by formula (I) includes, for example: hydrochloride, hydrobromide, hydroiodide, phosphate,

phosphonate and sulfate; sulfonates such as methanesulfonate and p-toluenesulfonate; carboxylate such as acetate, citrate, malate, tartrate, succinate and salicylate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; and ammonium salts such as ammonium salt, alkylammonium salt, dialkylammonium salt, trialkylammonium salt and tetraalkylammonium salt. Preferred examples include hydrochloride and methanesulfonate. Hydrochloride is more preferred.

Such a salt is produced by contacting the compound with an acid or a base available in pharmaceutical production.

In the present invention, the compound represented by formula (I) or the salt thereof may be anhydrous or may form a solvate such as a hydrate. The term "solvation" used herein refers to a phenomenon where solute molecules or ions in a solution strongly attract solvent molecules adjacent thereto to create one molecular population and refers to, for example, hydration if the solvent is water. The solvate may be a hydrate or a non-hydrate. An alcohol (e.g., methanol, ethanol, n-propanol), dimethylformamide, or the like can be used as the non-hydrate.

[0042]

Also, the compound or the salt thereof used in the present invention can exist in some tautomeric forms, for example, enol and imine forms, keto and enamine forms and mixtures thereof. The tautomers exist as a mixture of tautomeric sets in a solution. One tautomer is usually dominant in a solid form. The expression "one tautomer" in the present invention includes all tautomers of the compound used in the present invention.

The present invention includes all of stereoisomers (e.g., enantiomers, diastereomers (including cis and trans geometric isomers)) of the compound represented by formula (I), racemates of the isomers and other mixtures. The compound used in the present invention may have, for example, one or more asymmetric points in formula (I). The present invention includes racemic mixtures, diastereomeric mixtures and enantiomers of such compounds.

The compound according to the present invention may be obtained in a free form. In such a case, the free form can be converted to a salt that may be formed by the compound or to a hydrate or solvate thereof according to a routine method.

Alternatively, the compound according to the present invention may be obtained as a salt, hydrate or solvate of the compound. In such a case, these forms can be converted to a free form of the compound according to a routine method.

[0043]

Also, a substance used in the present invention includes a prodrug of the compound of formula (I). In this context, the term "prodrug" is intended to mean a derivative of the compound of formula (I) that is converted to the compound of formula (I) or a pharmaceutically acceptable salt thereof through enzymatic or nonenzymatic degradation under physiological conditions after administration. The prodrug may be inactive when administered to a patient, but exists *in vivo* as the active compound of formula (I) converted therefrom.

The prodrug, for example, converts to a desired drug form when a specific pH is reached or through the action of an enzyme.

[0044]

Typical production method

The compound represented by formula (I) that serves as the active ingredient of the therapeutic or prophylactic agent of the present invention can be produced according to a method described in International Publication No. WO2010/143664, though the method for producing the compound represented by formula (I) is not limited thereto.

[0045]

Therapeutic and/or prophylactic agent of the present invention

The term "therapeutic and/or prophylactic agent" used in the present invention refers to a pharmaceutical agent that is used for treatment or prevention or for treatment and prevention and specifically refers to a pharmaceutical agent that is used, for example, for treating or preventing the target disease or for suppressing progression (preventing exacerbations or maintaining the status quo) of the disease state.

The therapeutic and/or prophylactic agent of the present invention can be used as a pharmaceutical composition comprising a selected compound useful for the present invention and additionally a pharmaceutically acceptable carrier.

The term "pharmaceutically acceptable carrier" used herein is intended to mean one or more compatible solid or liquid excipients or encapsulating materials that are suitable for administration to mammals. The term "acceptable" used herein is intended to mean that the compound of interest and other ingredients are miscible in a composition in such a manner that reaction substantially reducing the pharmaceutical effectiveness of the composition does not occur therebetween under ordinary use conditions. As a matter of course, the pharmaceutically acceptable carrier must have sufficiently high purity and sufficiently low toxicity suitable for administration to, preferably an animal, more preferably a mammal, to be treated.

[0046]

Examples of a material that may be used as the pharmaceutically acceptable carrier include: sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as carboxymethylcellulose sodium, ethylcellulose and methylcellulose; tragacanth gum powder; malt; gelatin; talc; solid lubricants such as stearic acid and magnesium stearate; calcium sulfate; plant oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and cacao oil; polyhydric alcohols such as propylene glycol, glycerin, sorbitol, mannitol and polyethylene glycol; alginic acid; emulsifiers such as TWEEN; wetting agents such as lecithin; colorants; flavors; tableting agents; stabilizers; antioxidants; antiseptics; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

Examples of a method for administering the therapeutic and/or prophylactic agent of the present invention include oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intravesical and local (drip, powder, ointment, gel or cream) routes and inhalation (into oral cavity or using nasal sprays). Examples of the dosage form thereof include: solid preparations such as tablets, capsules, granules, powders and pills; liquid preparations such as aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions charged in containers adapted to division into individual doses; and freeze-dried preparations that can be dissolved in use. Alternatively, the dosage form may be adapted to various administration methods encompassing controlled-release formulations as in subcutaneous implantation.

[0047]

These preparations are produced by a well known method using additives such as excipients, lubricants (coating agents), binders, disintegrants, stabilizers, flavoring agents and diluents.

Examples of the excipients can include starches such as starch, potato starch and corn starch, lactose, crystalline cellulose and calcium hydrogen phosphate.

Examples of the coating agents can include ethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, shellac, talc, carnauba wax and paraffin.

Examples of the binders can include polyvinylpyrrolidone, Macrogol and the compounds similar to the excipients.

Examples of the disintegrants can include compounds similar to the excipients and chemically modified starches and celluloses such as croscarmellose sodium, carboxymethyl starch sodium and cross-linked polyvinylpyrrolidone.

Examples of the stabilizers can include: p-hydroxybenzoate esters such as methylparaben and propylparaben; alcohols such as chlorobutanol, benzyl alcohol and phenylethyl alcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid.

Examples of the flavoring agents can include sweeteners, acidulants and flavors usually used.

The liquid preparations can be produced using a solvent such as ethanol, phenol, chlorocresol, purified water or distilled water.

Examples of the surfactants or emulsifiers can include polysorbate 80, polyoxyl 40 stearate, sodium lauryl sulfate and Lauromacrogol.

[0048]

The amount of the prophylactic and/or therapeutic agent of the present invention used differs depending on symptom, age, body weight, relative health conditions, the presence of other medications, administration methods, etc. In the case of oral agents, a general effective amount, for example, for a patient (warm-blooded animal, particularly a human) is preferably 0.001 to 3000 mg/kg body weight, more preferably 0.01 to 300 mg/kg body weight, per day in terms of the amount of the active ingredient (compound represented by formula (I)), and the daily dose in an adult patient having a normal body weight is in the range of preferably 1

to 800 mg. In the case of parenteral agents, a general effective amount is preferably 0.001 to 1000 mg/kg body weight, more preferably 0.01 to 300 mg/kg body weight, per day. Desirably, this amount is administered at a single dose or several divided doses per day according to symptom.

The prophylactic and/or therapeutic agent of the present invention may be formulated by a method described in International Publication No. WO2012/023597. [0049]

The therapeutic and/or prophylactic agent of the present invention may be used in combination with one or more pharmaceutical agents selected from, for example, other chemotherapeutic agents, hormone therapeutic agents, immunotherapeutic agents and molecular target drugs (hereinafter, collectively referred to as concomitant agents). Such an active ingredient may be a low-molecular-weight compound. Alternatively, such an active ingredient may be a low-molecular-weight compound, may be a high-molecular-weight protein, polypeptide or antibody, or may be a vaccine or the like. Moreover, two or more of these active ingredients may be mixed for use at an appropriate ratio.

Examples of the "chemotherapeutic agents" include alkylating agents, platinum preparations, metabolic antagonists, topoisomerase inhibitors, anticancer antibiotics and plant-derived anticancer agents. Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambucil, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosilate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, estramustine sodium phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, ethoglucid, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulfan, trofosfamide, zinostatin stimalamer, adozelesin, cystemustine and bizelesin. Examples of the "platinum preparations" include carboplatin, cisplatin, miboplatin, nedaplatin and oxaliplatin. Examples of the "metabolic antagonists" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, galocitabine, emitefur), aminopterin, leucovorin calcium, tabloid, butocin, calcium folinate, calcium

levofolinate, cladribine, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, tiazofurin and ambamustine. Examples of topoisomerase I inhibitors (e.g., irinotecan, topotecan), topoisomerase II inhibitors (e.g., sobuzoxane) and the "anticancer antibiotics" include anthracycline anticancer agents (doxorubicin hydrochloride, daunorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, etc.), actinomycin D, actinomycin C, mitomycin C, chromomycin A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, neocarzinostatin, mithramycin, sarkomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride and idarubicin hydrochloride. Examples of the "plant-derived anticancer agents" include vinca alkaloid anticancer agents (vinblastine sulfate, vincristine sulfate, vindesine sulfate, etc.), taxane anticancer agents (paclitaxel, docetaxel, etc.) etoposide, etoposide phosphate, teniposide and vinorelbine.

[0050]

Examples of the "hormone therapeutic agents" include adrenocortical hormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone). Among them, prednisolone is preferred.

Examples of the "immunotherapeutic agents (biological response modifiers: BRMs)" include Picibanil, Krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factors, granulocyte colony-stimulating factors, lymphotoxins, BCG vaccines, *Corynebacterium parvum*, levamisole, polysaccharide K and procodazole.

The "molecular target drugs" include, for example, "pharmaceutical agents that inhibit the action of cell growth factors and their receptors". The "cell growth factors" may be any substance that promotes cell growth, and examples typically include peptides with a molecular weight of 20,000 or lower which are factors that exert action at lower concentrations through binding to their receptors and specifically include (1) EGF (epidermal growth factor) and substances having substantially the same activity thereof [e.g., EGF, heregulin (HER2 ligand)], (2) insulin and substances having substantially the same activity thereof [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2], (3) FGF (fibroblast growth factor) and substances having substantially the same activity thereof [e.g., acidic FGF, basic

FGF, KGF (keratinocyte growth factor), FGF-10], (4) VEGF (vascular endothelial growth factor) and (5) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGF β (transforming growth factor β), HGF (hepatocyte growth factor)].

The "cell growth factor receptors" may be any receptor having the ability to bind to the above cell growth factors, and specific examples include EGF receptors, heregulin receptors (HER2), insulin receptors, IGF receptors, FGF receptor-1 or FGF receptor-2, HGF receptors (c-met), VEGF receptors and SCF receptors (c-kit). Examples of the "pharmaceutical agents that inhibit the action of cell growth factors" include Herceptin (HER2 antibody), GLEEVEC (c-kit, abl inhibitor) and Tarceva (EGF receptor inhibitor).

The molecular target drugs also include pharmaceutical agents each inhibiting the actions of a plurality of cell growth factors, and pharmaceutical agents that block intracellular signals generated by cell growth factors.

[0051]

In addition to the above pharmaceutical agents, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salts, mercury-hematoporphyrin sodium, differentiation inducers (e.g., retinoid, vitamin Ds), angiogenesis inhibitors, α -blockers (e.g., tamsulosin hydrochloride), and the like can also be used.

Among those described above, a platinum complex (e.g., carboplatin, cisplatin, oxaliplatin), a metabolic antagonist (e.g., gemcitabine, pemetrexed), a topoisomerase I inhibitor (e.g., irinotecan, topotecan), a plant-derived anticancer agent (taxane drugs (e.g., paclitaxel, docetaxel), vinorelbine), an anticancer antibiotic (e.g., mitomycin C), a hormone therapeutic agent (e.g., prednisolone), an immunotherapeutic agent (e.g., Picibanil, Krestin), a molecular target drug (e.g., anti-VEGF antibodies such as bevacizumab, EGFR inhibitors such as erlotinib, VEGFR inhibitors such as sunitinib), or the like is preferred as a concomitant agent. Cisplatin, gemcitabine, paclitaxel, bevacizumab, or the like is more preferred. Alternatively, the therapeutic and/or prophylactic agent of the present invention may be used in combination with a combination therapy using these pharmaceutical

agents. Examples include combined use with a combination therapy of cisplatin, vinblastine and mitomycin C, cisplatin and vinorelbine, cisplatin and paclitaxel, cisplatin and gemcitabine, carboplatin and paclitaxel, pemetrexed and cisplatin, or bevacizumab, cisplatin and pemetrexed.

[0052]

In the present invention, the timings of administration of the active ingredient of the present invention and the concomitant agent are not limited, and they may be administered simultaneously or at a time interval to a subject to be administered. Alternatively, the active ingredient of the present invention and the concomitant agent may be administered as a single preparation comprising them to a subject to be administered. For example, they may be administered by a multidrug therapy which involves drip-injecting a plurality of drugs in combination over 3 to 6 months or by a method which involves taking oral agents over approximately 2 years.

Also, a preoperative adjuvant therapy such as "chemotherapy" may be performed before execution of surgery in order to inhibit already spread tumor (cancer) cells to prevent recurrence as a result of metastasis or for the purpose of reducing the extent of surgery.

A postoperative adjuvant therapy such as "chemotherapy" may be further performed in order to inhibit the growth of tumor (cancer) cells that have not been removed by local treatment such as surgery or radiation to prevent recurrence as a result of metastasis.

The anticancer agent that may be used in combination with the active ingredient of the present invention may act on not only cancer cells but also normal cells, resulting in the occurrence of adverse reactions. Typical adverse reactions include nausea caused by gastrointestinal mucosal damage, vomiting, anorexia, stomatitis, diarrhea or constipation, taste abnormality, decrease in leukocyte, erythrocyte or platelet level or alopecia caused by bone marrow damage, immune compromise, etc. The active ingredient of the present invention and the concomitant agent may be used in combination with an adverse reaction-reducing agent in order to prevent these adverse reactions. Examples include antiemetics effectively suppressing nausea (e.g., granisetron hydrochloride) and drugs promoting recovery from bone marrow damage (e.g., erythropoietin, G-CSF, GM-CSF).

The dose of the concomitant agent can be appropriately selected with reference to a dose clinically used. The mixing ratio between the active ingredient of the present invention and the concomitant agent can be appropriately selected according to the subject to be administered, administration routes, the target disease, symptom, combination of the pharmaceutical agents, etc. For example, when the subject to be administered is a human, 0.01 to 100 parts by weight of the concomitant agent may be used with respect to 100 parts by weight of a preparation comprising the active ingredient of the present invention.

[0053]

Method for detecting mutation in RET

The therapeutic and/or prophylactic agent of the invention of the present application is expected to be therapeutically and/or prophylactically effective by administration to a subject confirmed to have a mutation in RET. This suggests that a patient confirmed to have a mutation in RET is sensitive to the therapeutic and/or prophylactic agent of the invention of the present application. In the present invention, the method for detecting a mutation in RET includes a method for detecting a mutation in RET gene and a method for detecting a mutation in RET protein.

The method for detecting a mutation in RET gene comprises the step of detecting the presence of a RET gene-related specific polynucleotide shown below in a sample obtained from the subject and the amplification of the specific polynucleotide.

Specifically, the method comprises the following steps (1) to (3):

- (1) A sample (blood, pulmonary alveolus, a biopsied sample, an expectoration sample, etc.) is taken from the subject;
- (2) Genomic DNA or a transcript thereof (e.g., mRNA, cDNA, protein) is extracted from the sample. The genomic DNA can be extracted by a method known in the art. This extraction can be conveniently performed using a commercially available DNA extraction kit.
- (3) The presence of a specific polynucleotide in the extracted genomic DNA or transcript thereof (e.g., mRNA, cDNA, protein) and the presence or absence of amplification of the specific polynucleotide are detected.

The presence of the specific polynucleotide can be detected using gene analysis methods known in the art (e.g., methods such as PCR, reverse transcription PCR, Sanger sequencing, *in situ* hybridization and microarray method) singly or in combination.

In the event of detecting the presence of the specific polynucleotide sequence by using mRNA, the detection can be performed by gene amplification reaction such as reverse transcription PCR using primers designed to be capable of specifically amplifying the polynucleotide sequence to be detected. The primer design can be performed using primer design software (e.g., Primer Express; PE Biosystems) or the like.

In addition, the PCR products which are obtained by PCR and reverse transcription PCR are analyzed by agarose gel electrophoresis, and the successful obtainment of an amplification fragment with a size of interest can be confirmed by ethidium bromide staining or the like. The successful obtainment of an amplification fragment with a size of interest shows that the specific polynucleotide is present in the sample obtained from the subject.

A point mutation, deletion mutation or insertion mutation in RET gene can be detected by detecting the presence of the specific polynucleotide using, for example, a combined method of the above reverse transcription PCR and Sanger sequencing, or a single-nucleotide extension reaction method known in the art.

[0054]

A fusion gene between RET gene and another gene can be detected by a method for detecting the presence of the specific polynucleotide using a combined method of the above reverse transcription PCR and Sanger sequencing or using an *in situ* hybridization technique. The detection using the *in situ* hybridization technique can be performed by, for example, fluorescent *in situ* hybridization (FISH), chromogenic *in situ* hybridization (CISH) or silver *in situ* hybridization (SISH) known in the art.

A probe which can be used in hybridization is a nucleic acid molecule of at least 32 consecutive nucleotides (16 upstream nucleotides and 16 downstream nucleotides flanking the fusion point) that hybridizes under stringent conditions (preferably under more stringent conditions) to the specific polynucleotide or its

complementary strand, but not limited to. A probe comprising the sequence of a specific portion in a polynucleotide having a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5 to 14, 25 and 26, or its complementary strand can also be used.

The stringent conditions can be determined on the basis of the melting temperature (T_m) of a nucleic acid to form a complex according to a routine method. Specifically, the stringent conditions involve "5 × SSPE, 5 × Denhardt's solution, 0.5% SDS, 50% formamide, 200 µg/ml salmon sperm DNA, 42°C overnight" as conditions for hybridization and "0.5 × SSC, 0.1% SDS, 42°C" as conditions for washing. More stringent conditions involve "5 × SSPE, 5 × Denhardt's solution, 0.5% SDS, 50% formamide, 200 µg/ml salmon sperm DNA, 42°C overnight" as conditions for hybridization and "0.2 × SSC, 0.1% SDS, 65°C" as conditions for washing.

[0055]

Detection of the amplification of RET gene can be conducted by detecting the amplification of the specific polynucleotide by the above *in situ* hybridization technique or by comparative genomic hybridization (CGH) using genomic DNA.

The specific polynucleotide to be detected refers to a polynucleotide having a base varied due to a point mutation, deletion mutation or insertion mutation in polynucleotide constituting RET gene, a polynucleotide constituting the fusion gene between RET gene and another gene (e.g., KIF5B gene, CCDC6 gene, NCOA4 gene, TRIM33 gene), or amplified polynucleotide constituting RET gene. Examples of such a polynucleotide include, but are not limited to, the polynucleotides shown below and polynucleotides hybridizing under stringent conditions to polynucleotides consisting of sequences complementary to these polynucleotides (particularly polynucleotides encoding polypeptides having tyrosine kinase activity).

(1) Polynucleotide constituting fusion gene between RET gene and KIF5B gene:

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 5

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 6

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 7

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 8

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 9

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 10

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 11

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 12

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 13

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 14

(2) Polynucleotide constituting fusion gene between RET gen and CCDC6 gene:

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 25

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 26

(3) Polynucleotide constituting RET gene:

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 1

Polynucleotide comprising the nucleotide sequence shown in SEQ ID NO: 2

(4) Polynucleotide having a base varied due to a point mutation, deletion mutation or insertion mutation in polynucleotide constituting RET gene:

Polynucleotide comprising a nucleotide sequence with a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A, 2600G, 2861T or 2943T (e.g., 2091G>T, 2261G>A, 2494G>C, 2562A>T, 2600G>A, 2600G>C, 2861T>G or 2943T>C mutation) of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1

Polynucleotide comprising a polynucleotide encoding a polypeptide with a mutation in the amino acid C609, C611, C618, C620, C630, C634, E768, V804, S891, A883 or M918 (e.g., C634W, C634Y, E768D, V804M, V804L or M918T mutation) of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3 [0056]

The method for detecting a mutation in RET further includes a method for detecting a mutation in RET protein in addition to the above method.

The method for detecting a mutation in RET comprises the step of detecting the presence of a specific polypeptide (hereinafter, referred to as a polypeptide to be detected) in a sample obtained from the subject. The step of detecting a polypeptide to be detected involves preparing a lysate from a sample obtained from the subject (e.g., cancer tissues or cells obtained from the subject).

In the event that a polypeptide to be detected is fusion protein between RET protein and another protein, the presence of polypeptide to be detected can be detected by

for example, immunoassay or enzyme activity assay using an antibody against KIF5B, CCDC6, NCOA4 or TRIM33 and an anti-RET antibody in combination. Preferably, an approach such as enzyme immunoassay, two-antibody sandwich ELISA, fluorescent immunoassay, radioimmunoassay or Western blotting using a monoclonal or polyclonal antibody specific for the polypeptide to be detected can be used. In addition to above mentioned method, detection of a mutation (including a point mutation, a deletion mutation and an insertion mutation) in RET protein can be conducted by detecting the presence of a polypeptide to be detected using Western blotting, mass spectrometry, or the like.

[0057]

Examples of the polypeptide to be detected include, but are not limited to, the polypeptides shown below and polypeptides with deletion, substitution and/or insertion of one or more amino acids (e.g., 1 to 10, 1 to 5, or 1 to 3 amino acids) in these polypeptides (particularly polypeptides having tyrosine kinase activity).

(1) Polypeptide constituting fusion protein between RET protein and KIF5B protein:

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 15

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 16

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 17

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 18

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 19

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 20

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 21

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 22

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 23

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 24

(2) Polypeptide constituting fusion protein between RET protein and CCDC6 protein:

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 27

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 28

(3) Polypeptide constituting RET protein

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 3

Polypeptide comprising the amino acid sequence shown in SEQ ID NO: 4

(4) Polypeptide having a point mutation in a polypeptide constituting RET protein

Polypeptide encoded by a polynucleotide comprising a nucleotide sequence with a mutation in the nucleotide 2091G, 2261G, 2494G, 2562A, 2600G, 2861T or 2943T (e.g., 2091G>T, 2261G>A, 2494G>C, 2562A>T, 2600G>A, 2600G>C, 2861T>G or 2943T>C mutation) of a polynucleotide having the nucleotide sequence shown in SEQ ID NO: 1

Polypeptide with a mutation in the amino acid C609, C611, C618, C620, C630, C634, G691, E768, Y791, V804, S891, A883 or M918 (e.g., C634W, C634Y, G691S, E768D, Y791F, V804M, V804L, S891A or M918T mutation) of a polypeptide having the amino acid sequence shown in SEQ ID NO: 3
[0058]

In addition, the presence of the fusion gene between RET gene and KIF5B gene or other fusion genes can be detected by methods described in International Publication No. WO2012/014795, Nature Medicine, 2012, 18, p. 378-381, J Clin Oncol, 30 (35), Dec 10, 2012, p. 4352-9, Cancer Discov 2013 Jun, 3 (6), Jun 2013, p. 630-5, etc.

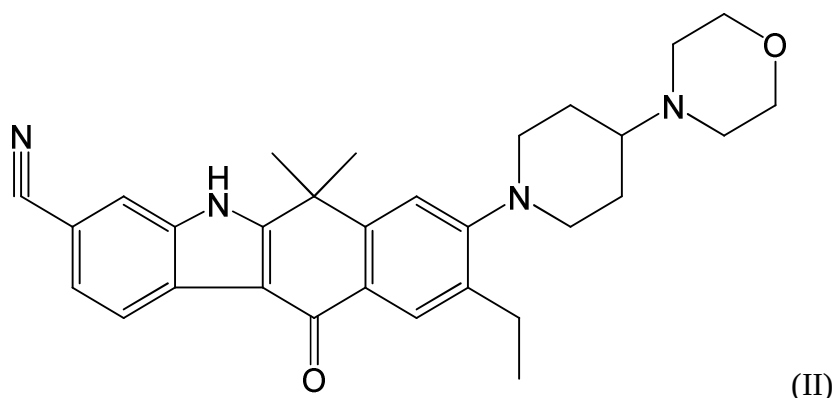
In addition to the above method, the activation of RET tyrosine kinase may be detected. The activation of RET tyrosine kinase can be confirmed by detecting phosphorylated RET in a tumor tissue by immunostaining or the like using an anti-phosphorylated RET antibody.

Examples

[0059]

Hereinafter, the present invention will be described more specifically with reference to Examples. However, the present invention is not intended to be limited to these Examples.

Compound 1 (9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, or 9-ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile) represented by formula II (compound described in Example 366 of WO2010/143664) was subjected to pharmacological tests described in Examples 1 to 6.



[0060]

Example 1

Evaluation of RET kinase inhibitory activity and binding affinity

The RET kinase inhibitory activity of compound 1 was evaluated with inhibitory activity against the phosphorylation reaction of a biotinylated peptide (EGPWLEEEEEAYGWMDf) as an index using RET kinase containing a N-terminally GST-tagged RET kinase domain (Carna Biosciences). The phosphorylated biotinylated peptide was detected by the TR-FRET (time-resolved fluorescence resonance energy transfer) method using an europium labeled anti-phosphorylation antibody. 50% inhibition concentration (IC₅₀ value) was calculated by the logistic regression method. As a result, compound 1 exhibited RET kinase inhibitory activity with an IC₅₀ value of 4.8 nM.

The dissociation constant (*K_d* value) of compound 1 for RET kinase was also measured by KINOME_{SCAN}(TM) (DiscoverX). As a result, compound 1 exhibited binding affinity to RET with *K_d* value of 7.6 nM.

[0061]

Example 2

Establishment of KIF5B-RET-expressing cells and evaluation of cell growth inhibitory activity against these cells

An expression plasmid CS-GS104J-M67 (GeneCopoeia) containing KIF5B-RET variant 1 (gene in which a region from the N-terminus of KIF5B CDS to exon 15 was fused with a region from exon 12 of RET CDS to the C-terminus) (SEQ ID NO: 5) was transfected into mouse lymphocytes Ba/F3 (RIKEN Cell Bank) by electroporation. After transfection, the cells were cultured overnight in an RPMI-1640 medium (Sigma-Aldrich) containing 10% FBS (Bovogen Biologicals) and 1

ng/mL recombinant mouse IL-3 (R&D systems). Then, the culture supernatant was replaced with an RPMI-1640 medium containing 10% FBS. The cells were seeded into a 96-well plate by the limiting dilution method. Approximately 2 weeks later, the expression of phosphorylated RET in cells grown in the absence of IL-3 was detected by Western blotting. This was used as an index to establish a cell line Ba/F3 KIF5B-RET stably expressing KIF5B-RET.

The Ba/F3 KIF5B-RET cells were seeded into a 96-well plate at a concentration of 2,500 cells/well in an RPMI-1640 medium containing 10% FBS. A hydrochloride salt of compound 1 was diluted to 1 nM to 10 μ M (final concentrations) with dimethyl sulfoxide and added to the 96-well plate. Dimethyl sulfoxide was added as a negative control. After culture at 37°C for 2 days in the presence of 5% CO₂, a cell counting reagent CellTiter-Glo(R) Luminescent Cell Viability Assay (Promega Corporation) was added thereto and stirred, followed by the measurement of luminescence intensity using a luminescence measurement apparatus Envision (PerkinElmer). The measurement value in a well supplemented with only a medium was defined as a cell viability of 0%, while the measurement value in a well supplemented with dimethyl sulfoxide was defined as a cell viability of 100%. The cell viability of the Ba/F3 KIF5B-RET cells was calculated at each concentration of compound 1. The IC₅₀ value was determined from the obtained values by the logistic regression method. As a result, compound 1 inhibited cell growth of Ba/F3 KIF5B-RET cells with IC₅₀ value of 86 nM.

These results demonstrated that compound 1 can inhibit the kinase activity of RET and can inhibit the growth of a cell line expressing KIF5B-RET.

[0062]

Example 3

Evaluation of cell growth inhibitory activity against thyroid medullary cancer cell line TT

Cell growth inhibitory activity was evaluated using a thyroid medullary cancer cell line TT (American Type Culture Collection) with a RET kinase active mutation (C634W).

The TT cells were seeded into a 96-well plate at a concentration of 5,000 cells/well in F-12K Nutrient Mixture (Life Technologies Corporation) containing

10% FBS and cultured overnight at 37°C in the presence of 5% CO₂. Then, a hydrochloride salt of compound 1 was diluted to 1 nM to 10 µM (final concentrations) with dimethyl sulfoxide and added to the 96-well plate. Dimethyl sulfoxide was added as a negative control. After culture at 37°C for 5 days in the presence of 5% CO₂, a cell counting reagent CellTiter-Glo(R) Luminescent Cell Viability Assay was added thereto and stirred, followed by the measurement of luminescence intensity using a luminescence measurement apparatus Envision. The measurement value in a well supplemented with only a medium was defined as a cell viability of 0%, while the measurement value in a well supplemented with dimethyl sulfoxide was defined as a survival rate of 100%. The cell viability of the TT cells was calculated at each concentration of compound 1. The IC₅₀ value was determined from the obtained values by the logistic regression method. As a result, compound 1 inhibited cell growth of TT cells with IC₅₀ value of 190 nM. .

[0063]

Example 4

RET kinase mutant inhibitory activity

The RET kinase mutant inhibitory activity of compound 1 was evaluated with inhibitory activity against the phosphorylation reaction of a biotinylated peptide (EGPWLEEEEEAYGWMDf) as an index using a RET kinase mutant containing a N-terminally GST-tagged RET kinase domain (Carna Biosciences, Millipore). The phosphorylated biotinylated peptide was detected by the TR-FRET method using an europium labeled anti-phosphorylation antibody. The IC₅₀ value was calculated by the logistic regression method. The test results are shown in Table 1. Compound 1 exhibited inhibitory activity against each mutant of RET kinase with a mutation (V804L, V804M) in a gatekeeper residue.

[Table 1]

RET mutant	IC ₅₀ (nM)
RET G691S	9.5
RET Y791F	14
RET V804L	32
RET V804M	53

RET S891A	8.3
RET M918T	5.7

[0064]

Example 5

Evaluation of cell growth inhibitory activity against non-small cell lung cancer cell line LC-2/ad

Cell growth inhibitory activity was evaluated using a non-small cell lung cancer cell line LC-2/ad (RIKEN, J Thorac Oncol. 2012 Dec, 7 (12), 1872-6) harboring CCDC6-RET fusion gene.

The LC-2/ad cells were seeded into a 96-well plate at a concentration of 2,000 cells/well in a medium of a 1:1 mixture of RPMI-1640 and Ham containing 15% FBS and 25 mM HEPES and cultured overnight at 37°C in the presence of 5% CO₂. Then, a hydrochloride salt of compound 1 was diluted to 1 nM to 1 μM (final concentrations) with dimethyl sulfoxide and added to the 96-well plate. Dimethyl sulfoxide was added as a negative control. After culture at 37°C for 5 days in the presence of 5% CO₂, a cell counting reagent CellTiter-Glo(R) Luminescent Cell Viability Assay was added thereto and stirred, followed by the measurement of luminescence intensity using a luminescence measurement apparatus Envision. The measurement value in a well supplemented with only a medium was defined as a cell viability of 0%, while the measurement value in a well supplemented with dimethyl sulfoxide was defined as a cell viability of 100%. The cell viability of the LC-2/ad cells was calculated at each concentration of compound 1. The IC₅₀ value was determined from the obtained values by the logistic regression method. As a result, compound 1 inhibited cell growth of LC-2/ad cells with IC₅₀ value of 190 nM.

[0065]

Example 6

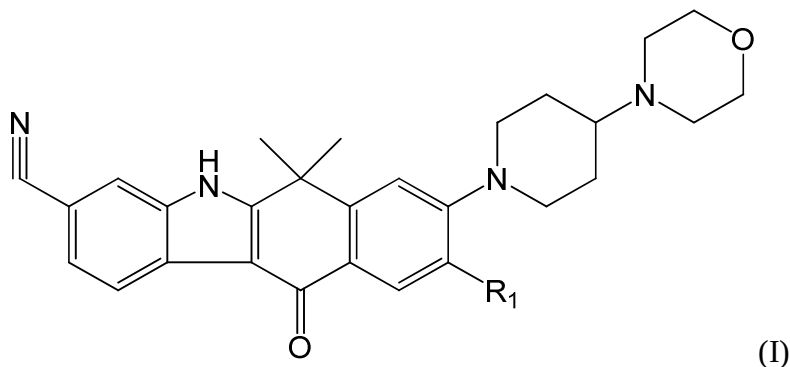
Evaluation of antitumor activity in xenograft mouse model harboring CCDC6-RET fusion gene

The *in vivo* antitumor activity of compound 1 was evaluated in non-small cell lung cancer cell line LC-2/ad-implanted mouse models. LC-2/ad was subcutaneously implanted to SCID mice and randomized after tumor size reached

200 to 350 mm³. The administration of the compound was started on the day of randomization. The vehicles used for dissolving the compound were 0.02 N HCl, 10% dimethyl sulfoxide, 10% Cremophor EL, 15% PEG400 and 15% HPCD (2-hydroxypropyl- β -cyclodextrin) (indicated by final concentration). Compound 1 was orally administered once a day to each mouse at a dose of 20 mg/kg or 60 mg/kg for 14 days. As a result, a dose-dependent tumor growth inhibitory effect and tumor regression were confirmed for all tumors. During this test, a significant body weight loss of a mouse was not observed at any dose. The results about the antitumor activity are shown in FIG. 1.

CLAIMS

1 A therapeutic and/or prophylactic agent for a tumor with a mutation in RET and for metastasis of the tumor, which comprises a compound represented by formula (I), a salt thereof or a solvate thereof as an active ingredient:



wherein R₁ is a C₁₋₆ alkyl group.

2 The therapeutic and/or prophylactic agent according to claim 1, wherein the tumor is selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, brain tumor, neuroblastoma, glioma, thyroid cancer, myelodysplastic syndrome, head and neck cancer, esophageal cancer, gastric cancer, colorectal cancer, breast cancer, ovarian cancer, lung cancer, pancreatic cancer, liver cancer, gallbladder cancer, skin cancer, malignant melanoma, kidney cancer, renal pelvic and ureteral cancer, bladder cancer, uterine cancer, testicular cancer, prostate cancer, and tumors metastasized from these tumors.

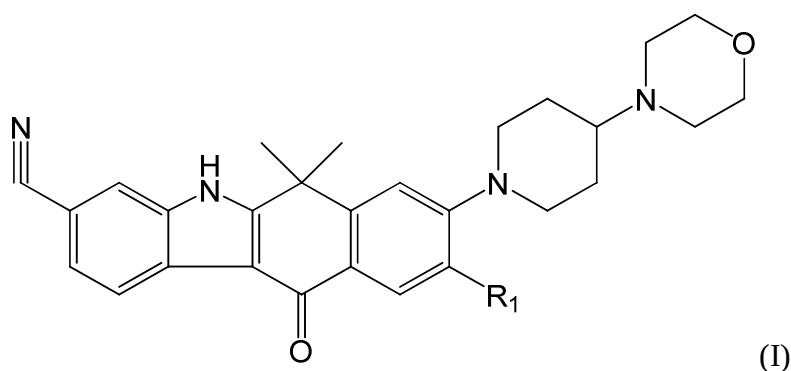
3 The therapeutic and/or prophylactic agent according to claim 1, wherein the tumor is thyroid cancer or lung cancer.

4 The therapeutic and/or prophylactic agent according to claim 1, wherein the tumor is thyroid medullary cancer or non-small cell lung cancer.

5 The therapeutic and/or prophylactic agent according to any one of claims 1 to 4, wherein the tumor is a tumor with a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

6 The therapeutic and/or prophylactic agent according to any one of claims 1 to 4, wherein the tumor is a tumor with a point mutation in RET gene and/or protein.

7 A therapeutic and/or prophylactic agent for a tumor used for a patient with a mutation in RET and for metastasis of the tumor, which comprises a compound represented by formula (I), a salt thereof or a solvate thereof as an active ingredient:



wherein R₁ is a C₁₋₆ alkyl group.

8 The therapeutic and/or prophylactic agent according to claim 7, wherein the tumor is thyroid cancer or lung cancer.

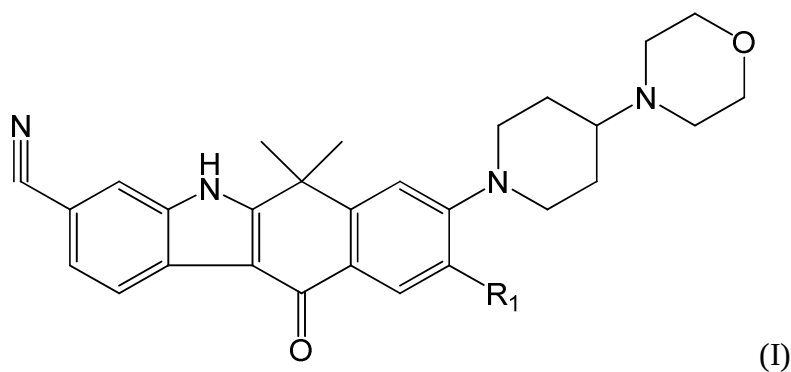
9 The therapeutic and/or prophylactic agent according to claim 7 or 8, wherein the patient is a patient with a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

10 The therapeutic and/or prophylactic agent according to claim 7 or 8, wherein the patient is a patient with a point mutation in RET gene and/or protein.

11 The therapeutic and/or prophylactic agent according to any one of claims 1 to 9, wherein R¹ is ethyl.

12 The therapeutic and/or prophylactic agent according to any one of claims 1 to 11, wherein the compound is a hydrochloride.

13 A RET inhibitor, which comprises a compound of formula (I), a salt thereof or a solvate thereof as an active ingredient:

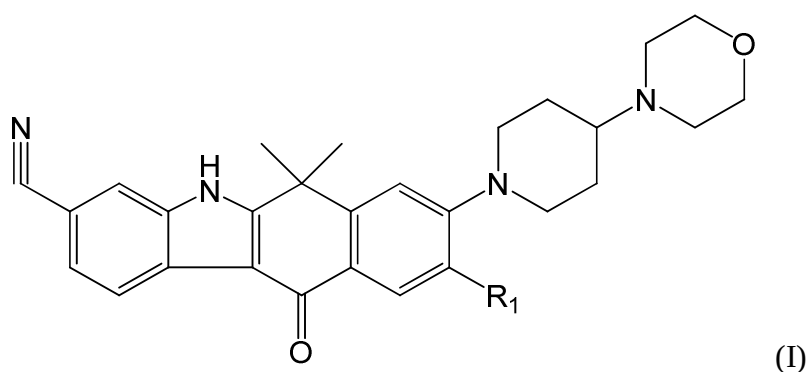


wherein R₁ is a C₁₋₆ alkyl group.

14 A method for identifying a patient sensitive to a compound represented by formula (I), a salt thereof or a solvate thereof, which comprises the steps of:

detecting the presence of a mutation in RET in a sample obtained from the patient; and

determining or preliminarily determining that the patient has sensitivity to the compound, the salt thereof or the solvate thereof, on the basis of the presence of a mutation in RET in the sample:



wherein R¹ is a C₁₋₆ alkyl group.

15 The method according to claim 14, wherein the mutation in RET is a mutation which induces activation of RET tyrosine kinase.

16 The method according to claim 14 or 15, wherein the mutation in RET is (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) the formation of a fusion gene of RET and/or a fusion protein of RET.

17 The method according to any one of claims 14 to 16, wherein the tumor is a tumor with a fusion gene of RET and/or a fusion protein of RET.

18 The method according to claim 14 or 15 wherein the mutation in RET is (a) a mutation in the cysteine-rich domain of RET tyrosine kinase, (b) a mutation in the tyrosine kinase domain of RET tyrosine kinase, or (c) the formation of a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

19 The method according to claim 14, 15 or 18, wherein the mutation in RET results in the formation of a fusion gene between RET gene and another gene and/or a fusion protein between RET protein and another protein.

20 The method according to claim 19, wherein the another gene and protein is KIF5B, CCDC6, NCOA4 or TRIM33.

21 The method according to any one of claims 18 to 20, wherein the fusion gene between RET gene and another gene and the fusion protein between RET protein and another protein comprise the tyrosine kinase domain of RET gene or protein and the coiled-coil domain of another gene or protein.

22 The method according to claim 14 or 15, wherein the mutation in RET is a point mutation.

23 The method according to claim 22, wherein the point mutation is a point mutation in the cysteine-rich domain or in the tyrosine kinase domain of RET tyrosine kinase.

24 The method according to any one of claims 14 to 23, wherein the patient is a patient with thyroid cancer or lung cancer.

25 The method according to any one of claims 14 to 24, wherein the patient is a patient with thyroid medullary cancer or non-small cell lung cancer.

JPOXMLDOC01-seq1
SEQUENCE LISTING

<110> Chugai Seiyaku Kabushiki Kaisha

<120> RET Inhibitor

<130> PCT13-0036

<150> JP2012-211040

<151> 2012-09-25

<160> 46

<170> PatentIn version 3.5

<210> 1

<211> 4174

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> RET transcript variant 4 (NM_020630.4)

<400> 1

agtcccgcga ccgaagcagg gcgcgcagca gcgctgagtg ccccggaacg tgcgtcgcgc	60
ccccagtgtc cgtcgcgtcc gccgcgcccc gggcggggat ggggcggcca gactgagcgc	120
cgcacccgcc atccagaccc gccggcccta gccgcagtcc ctccagccgt ggccccagcg	180
cgcacgggcg atggcgaagg cgacgtccgg tgccgcgggg ctgctgtctgc tgttgctgct	240
gctgctgccg ctgctaggca aagtggcatt gggcctctac ttctcgaggg atgcttactg	300
ggagaagctg tatgtggacc aggcggccgg cacgcccttg ctgtacgtcc atgccctgcg	360
ggacgcccct gaggaggtgc ccagcttccg cctggggccag catctctacg gcacgtaccg	420
cacacggctg catgagaaca actggatctg catccaggag gacaccggcc tcctctacct	480
taaccggagc ctggaccata gctcctggga gaagctcagt gtccgcaacc gcggctttcc	540
cctgctcacc gtctacctca aggtcttcct gtcacccaca tcccttcgtg agggcgagtg	600
ccagtggcca ggctgtgccc gcgtatactt ctccttcttc aacacctcct ttccagcctg	660
cagctccctc aagccccggg agctctgctt cccagagaca aggccctcct tccgcattcg	720
ggagaaccga ccccaggca ccttcacca gttccgcctg ctgcctgtgc agttcttggtg	780
ccccaacatc agcgtggcct acaggctcct ggagggtgag ggtctgccct tccgctgcgc	840
cccggacagc ctggaggtga gcacgcgctg ggccctggac cgcgagcagc gggagaagta	900
cgagctggtg gccgtgtgca ccgtgcacgc cggcgcgcg caggaggtgg tgatggtgcc	960
cttcccggtg accgtgtacg acgaggacga ctcggcgccc accttccccg cgggcgtcga	1020
caccgccagc gccgtggtgg agttcaagcg gaaggaggac accgtggtgg ccacgtgcg	1080
tgtcttcgat gcagacgtgg tacctgcac aggggagctg gtgaggcggt acacaagcac	1140
gctgctcccc ggggacacct gggcccagca gaccttccgg gtggaacact ggcccaacga	1200
gacctcggtc caggccaacg gcagcttcgt gcgggcgacc gtacatgact ataggctggt	1260

JPOXMLDOC01-seq1

tctcaaccgg	aacctctcca	tctcggagaa	ccgcaccatg	cagctggcgg	tgctggtcaa	1320
tgactcagac	ttccagggcc	caggagcggg	cgtcctcttg	ctccacttca	acgtgtcggg	1380
gctgccgggc	agcctgcacc	tgcccagtac	ctactccctc	tccgtgagca	ggagggctcg	1440
ccgatttgcc	cagatcggga	aagtctgtgt	ggaaaactgc	caggcattca	gtggcatcaa	1500
cgtccagtac	aagctgcatt	cctctggtgc	caactgcagc	acgctagggg	tggtcacctc	1560
agccgaggac	acctcgggga	tcctgtttgt	gaatgacacc	aaggccctgc	ggcggcccaa	1620
gtgtgccgaa	cttactaca	tggtggtggc	caccgaccag	cagacctcta	ggcaggccca	1680
ggcccagctg	cttgtaacag	tgagaggggtc	atatgtggcc	gaggaggcgg	gctgccccct	1740
gtcctgtgca	gtcagcaaga	gacggctgga	gtgtgaggag	tgtggcggcc	tggtgctcccc	1800
aacaggcagg	tgtgagtgga	ggcaaggaga	tggcaaaggg	atcaccagga	acttctccac	1860
ctgctctccc	agcaccaaga	cctgccccga	cggccactgc	gatgttgtgg	agaccaaga	1920
catcaacatt	tgccctcagg	actgcctccg	gggcagcatt	gttgggggac	acgagcctgg	1980
ggagccccgg	gggattaaag	ctggctatgg	cacctgcaac	tgcttccctg	aggaggagaa	2040
gtgcttctgc	gagcccgaag	acatccagga	tccactgtgc	gacgagctgt	gccgcacggt	2100
gatcgcagcc	gctgtcctct	tctccttcat	cgtctcgggtg	ctgctgtctg	ccttctgcat	2160
ccactgctac	cacaagtttg	cccacaagcc	acccatctcc	tcagctgaga	tgaccttccg	2220
gaggccccgc	caggccttcc	cggtcagcta	ctcctcttcc	ggtgccccgc	ggccctcgct	2280
ggactccatg	gagaaccagg	tctccgtgga	tgccttcaag	atcctggagg	atccaaagtg	2340
ggaattccct	cggaagaact	tggttcttgg	aaaaactcta	ggagaaggcg	aatttgaaa	2400
agtgggtcaag	gcaacggcct	tccatctgaa	aggcagagca	gggtacacca	cgggtggccgt	2460
gaagatgctg	aaagagaacg	cctccccgag	tgagcttcga	gacctgctgt	cagagttcaa	2520
cgtcctgaag	caggtcaacc	acccacatgt	catcaaattg	tatggggcct	gcagccagga	2580
tggcccgcctc	ctcctcatcg	tggagtacgc	caaatacggc	tccctgcggg	gcttctcccg	2640
cgagagccgc	aaagtggggc	ctggctacct	gggcagtgga	ggcagccgca	actccagctc	2700
cctggaccac	ccggatgagc	gggccctcac	catgggcgac	ctcatctcat	ttgcctggca	2760
gatctcacag	gggatgcagt	atctggccga	gatgaagctc	gttcatcggg	acttggcagc	2820
cagaaacatc	ctggtagctg	aggggaggaa	gatgaagatt	tcggatttctg	gcttgtccccg	2880
agatgtttat	gaagaggatt	cctacgtgaa	gaggagccag	ggtcggattc	cagttaaagt	2940
gatggcaatt	gaatcccttt	ttgatcatat	ctacaccacg	caaagtgatg	tatggtcttt	3000
tggtgtcctg	ctgtgggaga	tcgtgaccct	agggggaaac	ccctatcctg	ggattcctcc	3060
tgagcggctc	ttcaaccttc	tgaagaccgg	ccaccggatg	gagaggccag	acaactgcag	3120
cgaggagatg	taccgcctga	tgctgcaatg	ctggaagcag	gagccggaca	aaaggccggg	3180
gtttgcggac	atcagcaaag	acctggagaa	gatgatgggt	aagaggagag	actacttgga	3240
ccttgccggcg	tccactccat	ctgactccct	gatttatgac	gacggcctct	cagaggagga	3300

JPOXMLDOC01-seq1

gacaccgctg	gtggactgta	ataatgcccc	cctccctcga	gccctccctt	ccacatggat	3360
tgaaaacaaa	ctctatggta	gaatttccca	tgcatttact	agattctagc	accgctgtcc	3420
cctctgcact	atccttcctc	tctgtgatgc	tttttaaaaa	tgtttctggt	ctgaacaaaa	3480
ccaaagtctg	ctctgaacct	ttttatgtgt	aaatgtctga	ctttgcatcc	agtttacatt	3540
taggcattat	tgcaactatg	tttttctaaa	aggaagtga	aataagtgt	attaccacat	3600
tgcccagcaa	cttaggatgg	tagaggaaaa	aacagatcag	ggcggaactc	tcaggggaga	3660
ccaagaacag	gttgaataag	gcgcttctgg	ggtgggaatc	aagtcatagt	acttctactt	3720
taactaagtg	gataaatata	caaatctggg	gaggtattca	gttgagaaag	gagccaccag	3780
caccactcag	cctgcactgg	gagcacagcc	aggttcccc	agaccctcc	tgggcaggca	3840
ggtgcctctc	agaggccacc	cggcactggc	gagcagccac	tggccaagcc	tcagccccag	3900
tcccagccac	atgtcctcca	tcaggggtag	cgaggttgca	ggagctggct	ggccctggga	3960
ggacgcaccc	ccactgctgt	tttcacatcc	tttcccttac	ccaccttcag	gacggttgtc	4020
acttatgaag	tcagtgctaa	agctggagca	gttgcttttt	gaaagaacat	ggtctgtggt	4080
gctgtggtct	tacaatggac	agtaaatatg	gttcttgcca	aaactccttc	ttttgtcttt	4140
gattaaatac	tagaaattta	aaaaaaaaaa	aaaa			4174

<210> 2
 <211> 5629
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> RET transcript variant 2 (NM_020975.4)

<400> 2	
agtcccgcga	ccgaagcagg
gcgcgcagca	gcgctgagt
ccccggaacg	tgcgtcgcgc
60	
ccccagtgtc	cgtcgcgtcc
gccgcgcccc	ggcgggggat
ggggcgggcca	gactgagcgc
120	
cgcacccgcc	atccagaccc
gccggcccta	gccgcagtcc
ctccagccgt	ggccccagcg
180	
cgcacgggcg	atggcgaagg
cgacgtccgg	tgccgcgggg
ctgcgtctgc	tgttgtgct
240	
gctgctgccg	ctgctaggca
aagtggcatt	gggcctctac
ttctcgaggg	atgcttactg
300	
ggagaagctg	tatgtggacc
aggcgggccg	cacgcccttg
ctgtacgtcc	atgccctgcg
360	
ggacgccct	gaggaggtgc
ccagcttccg	cctggggcag
catctctacg	gcacgtaccg
420	
cacacggctg	catgagaaca
actggatctg	catccaggag
gacaccggcc	tcctctacct
480	
taaccggagc	ctggaccata
gctcctggga	gaagctcagt
gtccgcaacc	gcggctttcc
540	
cctgctcacc	gtctacctca
aggtcttcct	gtcaccaca
tcccttcgtg	agggcgagtg
600	
ccagtggcca	ggctgtgcc
gcgtatactt	ctccttcttc
aacacctcct	ttccagcctg
660	
cagctccctc	aagccccggg
agctctgctt	cccagagaca
aggccctcct	tccgcattcg
720	
ggagaaccga	ccccaggca
ccttcacca	gttccgcctg
ctgcctgtgc	agttcttggtg
780	

JPOXMLDOC01-seq1

ccccaacatc	agcgtggcct	acaggctcct	ggagggtgag	ggtctgccct	tccgctgcgc	840
cccggacagc	ctggaggtga	gcacgcgctg	ggccctggac	cgcgagcagc	gggagaagta	900
cgagctggtg	gccgtgtgca	ccgtgcacgc	cggcgcgcg	gaggaggtgg	tgatggtgcc	960
cttcccggtg	accgtgtacg	acgaggacga	ctcggcgccc	accttccccg	cgggcgtcga	1020
caccgccagc	gccgtggtgg	agttcaagcg	gaaggaggac	accgtggtgg	ccacgctgcg	1080
tgtcttcgat	gcagacgtgg	tacctgcac	aggggagctg	gtgaggcggt	acacaagcac	1140
gctgctcccc	ggggacacct	ggggccagca	gaccttcg	gtggaacact	ggcccaacga	1200
gacctcggtc	caggccaacg	gcagcttcgt	gcgggcgacc	gtacatgact	ataggctggt	1260
tctcaaccgg	aacctctcca	tctcggagaa	ccgcaccatg	cagctggcgg	tgctggtcaa	1320
tgactcagac	ttccaggggc	caggagcggg	cgctctcttg	ctccacttca	acgtgtcggt	1380
gctgccggtc	agcctgcacc	tgcccagtac	ctactccctc	tccgtgagca	ggagggctcg	1440
ccgatttgcc	cagatcggga	aagtctgtgt	ggaaaactgc	caggcattca	gtggcatcaa	1500
cgtccagtac	aagctgcatt	cctctggtgc	caactgcagc	acgctagggg	tggtcacctc	1560
agccgaggac	acctcgggga	tcctgtttgt	gaatgacacc	aaggccctgc	ggcggcccaa	1620
gtgtgccgaa	cttactaca	tggtggtggc	caccgaccag	cagacctcta	ggcaggccca	1680
ggcccagctg	cttgtaacag	tggaggggtc	atatgtggcc	gaggaggcgg	gctgccccct	1740
gtcctgtgca	gtcagcaaga	gacggctgga	gtgtgaggag	tgtggcggcc	tgggctcccc	1800
aacaggcagg	tgtgagtgga	ggcaaggaga	tggcaaagg	atcaccagga	acttctccac	1860
ctgctctccc	agcaccaaga	cctgccccga	cggccactgc	gatgttggtg	agaccaaga	1920
catcaacatt	tgccctcagg	actgcctccg	gggcagcatt	gttgggggac	acgagcctgg	1980
ggagccccgg	gggattaaag	ctggctatgg	cacctgcaac	tgcttccttg	aggaggagaa	2040
gtgcttctgc	gagcccgaag	acatccagga	tccactgtgc	gacgagctgt	gccgcacggt	2100
gatcgagcc	gctgtcctct	tctccttcac	cgctcgggtg	ctgctgtctg	ccttctgcat	2160
ccactgctac	cacaagtttg	cccacaagcc	acccatctcc	tcagctgaga	tgaccttccg	2220
gaggccccgc	caggccttcc	cggtcagcta	ctcctcttcc	ggtgcccgcc	ggccctcgct	2280
ggactccatg	gagaaccagg	tctccgtgga	tgccttcaag	atcctggagg	atccaaagtg	2340
ggaattccct	cgaagaact	tggttcttgg	aaaaactcta	ggagaaggcg	aatttgga	2400
agtggtaag	gcaacggcct	tccatctgaa	aggcagagca	gggtacacca	cgggtggccgt	2460
gaagatgctg	aaagagaacg	cctccccgag	tgagcttca	gacctgctgt	cagagttcaa	2520
cgctcctgaag	cagggtcaacc	accacatgt	catcaaattg	tatggggcct	gcagccagga	2580
tggcccgtc	ctcctcatcg	tggagtacgc	caaatacggc	tccctgcggg	gcttctccg	2640
cgagagccgc	aaagtggggc	ctggctacct	gggcagtgga	ggcagccgca	actccagctc	2700
cctggaccac	ccggatgagc	gggccctcac	catgggcgac	ctcatctcat	ttgcctggca	2760
gatctcacag	gggatgcagt	atctggccga	gatgaagctc	gttcatcggg	acttggcagc	2820

JPOXMLDOC01-seq1

cagaaacatc	ctggtagctg	aggggcgga	gatgaagatt	tcggatttcg	gcttgtccc	2880
agatgtttat	gaagaggatt	cctacgtgaa	gaggagccag	ggtcggattc	cagttaaagt	2940
gatggcaatt	gaatcccttt	ttgatcatat	ctacaccacg	caaagtgatg	tatggtcttt	3000
tgggtgtcctg	ctgtgggaga	tcgtgaccct	agggggaaac	ccctatcctg	ggattcctcc	3060
tgagcggctc	ttcaaccttc	tgaagaccgg	ccaccggatg	gagaggccag	acaactgcag	3120
cgaggagatg	taccgcctga	tgctgcaatg	ctggaagcag	gagccggaca	aaaggccggt	3180
gtttgctggac	atcagcaaag	acctggagaa	gatgatgggt	aagaggagag	actacttgga	3240
ccttgctggcg	tccactccat	ctgactccct	gatttatgac	gacggcctct	cagaggagga	3300
gacaccgctg	gtggactgta	ataatgcccc	cctccctcga	gccctccctt	ccacatggat	3360
tgaaaacaaa	ctctatggca	tgtcagaccc	gaactggcct	ggagagagtc	ctgtaccact	3420
cacgagagct	gatggcacta	acactgggtt	tccaagatat	ccaaatgata	gtgtatatgc	3480
taactggatg	ctttcacctt	cagcggcaaa	attaatggac	acgtttgata	gttaacattt	3540
ctttgtgaaa	ggtaatggac	tcacaagggg	aagaaacatg	ctgagaatgg	aaagtctacc	3600
ggccctttct	ttgtgaacgt	cacattggcc	gagccgtgtt	cagttcccag	gtggcagact	3660
cgtttttggt	agttttgttt	aacttccaag	gtggtttttac	ttctgatagc	cggtgatttt	3720
ccctcctagc	agacatgcca	caccgggtaa	gagctctgag	tcttagtggt	taagcattcc	3780
tttctcttca	gtgcccagca	gcacccagtg	ttggtctgtg	tccatcagtg	accaccaaca	3840
ttctgtgttc	acatgtgtgg	gtccaacact	tactacctgg	tgtatgaaat	tggacctgaa	3900
ctgttggtt	tttctagttg	ccgccaaaca	aggcaaaaaa	atttaaacad	gaagcacaca	3960
cacaaaaaag	gcagtaggaa	aaatgctggc	cctgatgacc	tgtccttatt	cagaatgaga	4020
gactgcgggg	ggggcctggg	ggtagtgtca	atgcccctcc	agggctggag	gggaagaggg	4080
gccccgagga	tgggcctggg	ctcagcattc	gagatcttga	gaatgatttt	tttttaatca	4140
tgcaaccttt	ccttaggaag	acatttggtt	ttcatcatga	ttaagatgat	tcctagattt	4200
agcacaatgg	agagattcca	tgccatcttt	actatgtgga	tgggtggtatc	agggagaggg	4260
gctcacaaga	cacatttgct	ccccggggcc	accacatcat	cctcacgtgt	tcggtactga	4320
gcagccacta	cccctgatga	gaacagtatg	aagaaagggg	gctgttgagg	tcccagaatt	4380
gctgacagca	gaggctttgc	tgctgtgaat	cccacctgcc	accagcctgc	agcacacccc	4440
acagccaagt	agaggcgaaa	gcagtggctc	atcctacctg	ttaggagcag	gtagggcttg	4500
tactcacttt	aatttgaaat	ttatcaactt	actcataaag	ggacaggcta	gctagctgtg	4560
ttagaagtag	caatgacaat	gaccaaggac	tgctacacct	ctgattacaa	ttctgatgtg	4620
aaaaagatgg	tgtttggttc	ttatagagcc	tgtgtgaaag	gcccattgat	cagctcttcc	4680
tgtgtttgta	atttaagtct	gctacaagat	gtttctgttt	cttagattct	gaccatgact	4740
cataagcttc	ttgtcattct	tcattgcttg	tttgtggtca	cagatgcaca	acactcctcc	4800
agtcttgtgg	gggcagcttt	tgggaagtct	cagcagctct	tctggctgtg	ttgtcagcac	4860

JPOXMLDOC01-seq1

tgtaacttcg cagaaaagag tcggattacc aaaacactgc ctgctcttca gacttaaagc	4920
actgatagga cttaaaatag tctcattcaa atactgtatt ttatataggc atttcacaaa	4980
aacagcaaaa ttgtggcatt ttgtgaggcc aaggcttgga tgcgtgtgta atagagcctt	5040
gtgggtgtgtg cgcacacacc cagagggaga gtttgaaaaa tgcttattgg acacgtaacc	5100
tggctctaatt ttgggctggt tttcagatac actgtgataa gttctttttac aaatatctat	5160
agacatggta aacttttgggt tttcagatat gcttaatgat agtcttacta aatgcagaaa	5220
taagaataaa ctttctcaaa ttattaaaaa tgcctacaca gtaagtgtga attgctgcaa	5280
cagggtttggt ctcaggaggg taagaactcc aggtctaaac agctgaccca gtgatgggga	5340
atttatcctt gaccaattta tccttgacca ataacctaatt tgtctattcc tgagttataa	5400
aagtcccat ctttattagc tctactggaa ttttcataca cgtaaatagca gaagttacta	5460
agtattaagt attactgagt attaagtagt aatctgtcag ttattaaaaat ttgtaaaatc	5520
tatttatgaa aggtcattaa accagatcat gttccttttt ttgtaatcaa ggtgactaag	5580
aaaatcagtt gtgtaaataa aatcatgtat cataaaaaaa aaaaaaaa	5629

<210> 3
 <211> 1072
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <223> RET isoform c precursor (NP_065681.1)
 <400> 3

Met Ala Lys Ala Thr Ser Gly Ala Ala Gly Leu Arg Leu Leu Leu Leu
 1 5 10 15

Leu Leu Leu Pro Leu Leu Gly Lys Val Ala Leu Gly Leu Tyr Phe Ser
 20 25 30

Arg Asp Ala Tyr Trp Glu Lys Leu Tyr Val Asp Gln Ala Ala Gly Thr
 35 40 45

Pro Leu Leu Tyr Val His Ala Leu Arg Asp Ala Pro Glu Glu Val Pro
 50 55 60

Ser Phe Arg Leu Gly Gln His Leu Tyr Gly Thr Tyr Arg Thr Arg Leu
 65 70 75 80

His Glu Asn Asn Trp Ile Cys Ile Gln Glu Asp Thr Gly Leu Leu Tyr
 85 90 95

Leu Asn Arg Ser Leu Asp His Ser Ser Trp Glu Lys Leu Ser Val Arg
 100 105 110

Asn Arg Gly Phe Pro Leu Leu Thr Val Tyr Leu Lys Val Phe Leu Ser

JPOXMLDOC01-seq1

115

120

125

Pro Thr Ser Leu Arg Glu Gly Glu Cys Gln Trp Pro Gly Cys Ala Arg
130 135 140

Val Tyr Phe Ser Phe Phe Asn Thr Ser Phe Pro Ala Cys Ser Ser Leu
145 150 155 160

Lys Pro Arg Glu Leu Cys Phe Pro Glu Thr Arg Pro Ser Phe Arg Ile
165 170 175

Arg Glu Asn Arg Pro Pro Gly Thr Phe His Gln Phe Arg Leu Leu Pro
180 185 190

Val Gln Phe Leu Cys Pro Asn Ile Ser Val Ala Tyr Arg Leu Leu Glu
195 200 205

Gly Glu Gly Leu Pro Phe Arg Cys Ala Pro Asp Ser Leu Glu Val Ser
210 215 220

Thr Arg Trp Ala Leu Asp Arg Glu Gln Arg Glu Lys Tyr Glu Leu Val
225 230 235 240

Ala Val Cys Thr Val His Ala Gly Ala Arg Glu Glu Val Val Met Val
245 250 255

Pro Phe Pro Val Thr Val Tyr Asp Glu Asp Asp Ser Ala Pro Thr Phe
260 265 270

Pro Ala Gly Val Asp Thr Ala Ser Ala Val Val Glu Phe Lys Arg Lys
275 280 285

Glu Asp Thr Val Val Ala Thr Leu Arg Val Phe Asp Ala Asp Val Val
290 295 300

Pro Ala Ser Gly Glu Leu Val Arg Arg Tyr Thr Ser Thr Leu Leu Pro
305 310 315 320

Gly Asp Thr Trp Ala Gln Gln Thr Phe Arg Val Glu His Trp Pro Asn
325 330 335

Glu Thr Ser Val Gln Ala Asn Gly Ser Phe Val Arg Ala Thr Val His
340 345 350

Asp Tyr Arg Leu Val Leu Asn Arg Asn Leu Ser Ile Ser Glu Asn Arg
355 360 365

Thr Met Gln Leu Ala Val Leu Val Asn Asp Ser Asp Phe Gln Gly Pro
370 375 380

Gly Ala Gly Val Leu Leu Leu His Phe Asn Val Ser Val Leu Pro Val

JPOXMLDOC01-seq1

Ile His Cys Tyr His Lys Phe Ala His Lys Pro Pro Ile Ser Ser Ala

JPOXMLDOC01-seq1

660

665

670

Glu Met Thr Phe Arg Arg Pro Ala Gln Ala Phe Pro Val Ser Tyr Ser
675 680 685

Ser Ser Gly Ala Arg Arg Pro Ser Leu Asp Ser Met Glu Asn Gln Val
690 695 700

Ser Val Asp Ala Phe Lys Ile Leu Glu Asp Pro Lys Trp Glu Phe Pro
705 710 715 720

Arg Lys Asn Leu Val Leu Gly Lys Thr Leu Gly Glu Gly Glu Phe Gly
725 730 735

Lys Val Val Lys Ala Thr Ala Phe His Leu Lys Gly Arg Ala Gly Tyr
740 745 750

Thr Thr Val Ala Val Lys Met Leu Lys Glu Asn Ala Ser Pro Ser Glu
755 760 765

Leu Arg Asp Leu Leu Ser Glu Phe Asn Val Leu Lys Gln Val Asn His
770 775 780

Pro His Val Ile Lys Leu Tyr Gly Ala Cys Ser Gln Asp Gly Pro Leu
785 790 795 800

Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly Ser Leu Arg Gly Phe Leu
805 810 815

Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr Leu Gly Ser Gly Gly Ser
820 825 830

Arg Asn Ser Ser Ser Leu Asp His Pro Asp Glu Arg Ala Leu Thr Met
835 840 845

Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile Ser Gln Gly Met Gln Tyr
850 855 860

Leu Ala Glu Met Lys Leu Val His Arg Asp Leu Ala Ala Arg Asn Ile
865 870 875 880

Leu Val Ala Glu Gly Arg Lys Met Lys Ile Ser Asp Phe Gly Leu Ser
885 890 895

Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val Lys Arg Ser Gln Gly Arg
900 905 910

Ile Pro Val Lys Trp Met Ala Ile Glu Ser Leu Phe Asp His Ile Tyr
915 920 925

Thr Thr Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile

JPOXMLDOC01-seq1

930

935

940

Val Thr Leu Gly Gly Asn Pro Tyr Pro Gly Ile Pro Pro Glu Arg Leu
945 950 955 960

Phe Asn Leu Leu Lys Thr Gly His Arg Met Glu Arg Pro Asp Asn Cys
965 970 975

Ser Glu Glu Met Tyr Arg Leu Met Leu Gln Cys Trp Lys Gln Glu Pro
980 985 990

Asp Lys Arg Pro Val Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys Met
995 1000 1005

Met Val Lys Arg Arg Asp Tyr Leu Asp Leu Ala Ala Ser Thr Pro
1010 1015 1020

Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu Thr
1025 1030 1035

Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu Pro
1040 1045 1050

Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Arg Ile Ser His Ala
1055 1060 1065

Phe Thr Arg Phe
1070

<210> 4
<211> 1114
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> RET isoform a precursor (NP_066124.1)

<400> 4

Met Ala Lys Ala Thr Ser Gly Ala Ala Gly Leu Arg Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Pro Leu Leu Gly Lys Val Ala Leu Gly Leu Tyr Phe Ser
20 25 30

Arg Asp Ala Tyr Trp Glu Lys Leu Tyr Val Asp Gln Ala Ala Gly Thr
35 40 45

Pro Leu Leu Tyr Val His Ala Leu Arg Asp Ala Pro Glu Glu Val Pro
50 55 60

Ser Phe Arg Leu Gly Gln His Leu Tyr Gly Thr Tyr Arg Thr Arg Leu
Page 10

JPOXMLDOC01-seq1

65 70 75 80
 His Glu Asn Asn Trp₈₅ Ile Cys Ile Gln Glu₉₀ Asp Thr Gly Leu₉₅ Leu Tyr
 Leu Asn Arg Ser₁₀₀ Leu Asp His Ser₁₀₅ Trp Glu Lys Leu₁₁₀ Ser Val Arg
 Asn Arg Gly₁₁₅ Phe Pro Leu Leu Thr₁₂₀ Val Tyr Leu Lys Val₁₂₅ Phe Leu Ser
 Pro Thr₁₃₀ Ser Leu Arg Glu Gly₁₃₅ Glu Cys Gln Trp Pro₁₄₀ Gly Cys Ala Arg
 Val₁₄₅ Tyr Phe Ser Phe Phe₁₅₀ Asn Thr Ser Phe Pro₁₅₅ Ala Cys Ser Ser Leu₁₆₀
 Lys Pro Arg Glu₁₆₅ Leu Cys Phe Pro Glu Thr₁₇₀ Arg Pro Ser Phe Arg₁₇₅ Ile
 Arg Glu Asn Arg₁₈₀ Pro Pro Gly Thr Phe₁₈₅ His Gln Phe Arg₁₉₀ Leu Leu Pro
 Val Gln Phe₁₉₅ Leu Cys Pro Asn Ile₂₀₀ Ser Val Ala Tyr Arg₂₀₅ Leu Leu Glu
 Gly Glu₂₁₀ Gly Leu Pro Phe Arg₂₁₅ Cys Ala Pro Asp Ser₂₂₀ Leu Glu Val Ser
 Thr₂₂₅ Arg Trp Ala Leu Asp₂₃₀ Arg Glu Gln Arg Glu₂₃₅ Lys Tyr Glu Leu Val₂₄₀
 Ala Val Cys Thr Val₂₄₅ His Ala Gly Ala Arg₂₅₀ Glu Glu Val Val Met₂₅₅ Val
 Pro Phe Pro Val₂₆₀ Thr Val Tyr Asp Glu₂₆₅ Asp Asp Ser Ala Pro₂₇₀ Thr Phe
 Pro Ala Gly₂₇₅ Val Asp Thr Ala Ser₂₈₀ Ala Val Val Glu Phe₂₈₅ Lys Arg Lys
 Glu Asp₂₉₀ Thr Val Val Ala Thr₂₉₅ Leu Arg Val Phe Asp₃₀₀ Ala Asp Val Val
 Pro₃₀₅ Ala Ser Gly Glu₃₁₀ Val Arg Arg Tyr Thr₃₁₅ Ser Thr Leu Leu Pro₃₂₀
 Gly Asp Thr Trp Ala₃₂₅ Gln Gln Thr Phe Arg₃₃₀ Val Glu His Trp Pro₃₃₅ Asn
 Glu Thr Ser Val Gln Ala Asn Gly Ser Phe Val Arg Ala Thr Val His
 Page 11

JPOXMLDOC01-seq1

340

345

350

Asp Tyr Arg₃₅₅ Leu Val Leu Asn Arg₃₆₀ Asn Leu Ser Ile Ser₃₆₅ Glu Asn Arg
 Thr Met₃₇₀ Gln Leu Ala Val Leu₃₇₅ Val Asn Asp Ser Asp₃₈₀ Phe Gln Gly Pro
 Gly₃₈₅ Ala Gly Val Leu Leu₃₉₀ Leu His Phe Asn Val₃₉₅ Ser Val Leu Pro Val₄₀₀
 Ser Leu His Leu Pro₄₀₅ Ser Thr Tyr Ser Leu₄₁₀ Ser Val Ser Arg Arg₄₁₅ Ala
 Arg Arg Phe Ala₄₂₀ Gln Ile Gly Lys Val₄₂₅ Cys Val Glu Asn Cys₄₃₀ Gln Ala
 Phe Ser Gly₄₃₅ Ile Asn Val Gln Tyr₄₄₀ Lys Leu His Ser Ser₄₄₅ Gly Ala Asn
 Cys Ser₄₅₀ Thr Leu Gly Val Val₄₅₅ Thr Ser Ala Glu Asp₄₆₀ Thr Ser Gly Ile
 Leu₄₆₅ Phe Val Asn Asp Thr₄₇₀ Lys Ala Leu Arg Arg₄₇₅ Pro Lys Cys Ala Glu₄₈₀
 Leu His Tyr Met Val₄₈₅ Val Ala Thr Asp Gln₄₉₀ Gln Thr Ser Arg Gln₄₉₅ Ala
 Gln Ala Gln Leu₅₀₀ Leu Val Thr Val Glu₅₀₅ Gly Ser Tyr Val Ala₅₁₀ Glu Glu
 Ala Gly Cys₅₁₅ Pro Leu Ser Cys Ala₅₂₀ Val Ser Lys Arg Arg₅₂₅ Leu Glu Cys
 Glu₅₃₀ Glu Cys Gly Gly Leu Gly₅₃₅ Ser Pro Thr Gly Arg₅₄₀ Cys Glu Trp Arg
 Gln₅₄₅ Gly Asp Gly Lys Gly₅₅₀ Ile Thr Arg Asn Phe₅₅₅ Ser Thr Cys Ser Pro₅₆₀
 Ser Thr Lys Thr Cys₅₆₅ Pro Asp Gly His Cys₅₇₀ Asp Val Val Glu Thr₅₇₅ Gln
 Asp Ile Asn Ile₅₈₀ Cys Pro Gln Asp Cys₅₈₅ Leu Arg Gly Ser Ile₅₉₀ Val Gly
 Gly His Glu₅₉₅ Pro Gly Glu Pro Arg₆₀₀ Gly Ile Lys Ala Gly₆₀₅ Tyr Gly Thr
 Cys Asn Cys Phe Pro Glu Glu Glu Lys Cys Phe Cys Glu Pro Glu Asp

JPOXMLDOC01-seq1

610

615

620

Ile Gln Asp Pro Leu Cys Asp Glu Leu Cys Arg Thr Val Ile Ala Ala
 625 630 635 640

Ala Val Leu Phe Ser Phe Ile Val Ser Val Leu Leu Ser Ala Phe Cys
 645 650 655

Ile His Cys Tyr His Lys Phe Ala His Lys Pro Pro Ile Ser Ser Ala
 660 665 670

Glu Met Thr Phe Arg Arg Pro Ala Gln Ala Phe Pro Val Ser Tyr Ser
 675 680 685

Ser Ser Gly Ala Arg Arg Pro Ser Leu Asp Ser Met Glu Asn Gln Val
 690 695 700

Ser Val Asp Ala Phe Lys Ile Leu Glu Asp Pro Lys Trp Glu Phe Pro
 705 710 715 720

Arg Lys Asn Leu Val Leu Gly Lys Thr Leu Gly Glu Gly Glu Phe Gly
 725 730 735

Lys Val Val Lys Ala Thr Ala Phe His Leu Lys Gly Arg Ala Gly Tyr
 740 745 750

Thr Thr Val Ala Val Lys Met Leu Lys Glu Asn Ala Ser Pro Ser Glu
 755 760 765

Leu Arg Asp Leu Leu Ser Glu Phe Asn Val Leu Lys Gln Val Asn His
 770 775 780

Pro His Val Ile Lys Leu Tyr Gly Ala Cys Ser Gln Asp Gly Pro Leu
 785 790 795 800

Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly Ser Leu Arg Gly Phe Leu
 805 810 815

Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr Leu Gly Ser Gly Gly Ser
 820 825 830

Arg Asn Ser Ser Ser Leu Asp His Pro Asp Glu Arg Ala Leu Thr Met
 835 840 845

Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile Ser Gln Gly Met Gln Tyr
 850 855 860

Leu Ala Glu Met Lys Leu Val His Arg Asp Leu Ala Ala Arg Asn Ile
 865 870 875 880

Leu Val Ala Glu Gly Arg Lys Met Lys Ile Ser Asp Phe Gly Leu Ser
 Page 13

JPOXMLDOC01-seq1

885

890

895

Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val Lys Arg Ser Gln Gly Arg
900 905 910

Ile Pro Val Lys Trp Met Ala Ile Glu Ser Leu Phe Asp His Ile Tyr
915 920 925

Thr Thr Gln Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile
930 935 940

Val Thr Leu Gly Gly Asn Pro Tyr Pro Gly Ile Pro Pro Glu Arg Leu
945 950 955 960

Phe Asn Leu Leu Lys Thr Gly His Arg Met Glu Arg Pro Asp Asn Cys
965 970 975

Ser Glu Glu Met Tyr Arg Leu Met Leu Gln Cys Trp Lys Gln Glu Pro
980 985 990

Asp Lys Arg Pro Val Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys Met
995 1000 1005

Met Val Lys Arg Arg Asp Tyr Leu Asp Leu Ala Ala Ser Thr Pro
1010 1015 1020

Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu Thr
1025 1030 1035

Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu Pro
1040 1045 1050

Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Met Ser Asp Pro Asn
1055 1060 1065

Trp Pro Gly Glu Ser Pro Val Pro Leu Thr Arg Ala Asp Gly Thr
1070 1075 1080

Asn Thr Gly Phe Pro Arg Tyr Pro Asn Asp Ser Val Tyr Ala Asn
1085 1090 1095

Trp Met Leu Ser Pro Ser Ala Ala Lys Leu Met Asp Thr Phe Asp
1100 1105 1110

Ser

<210> 5
<211> 2808
<212> DNA
<213> Homo sapiens

JPOXMLDOC01-seq1

<220>

<221> misc_feature

<223> KIF5B-RET (K15;R12 variant 4)

<400> 5

atggcggacc tggccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag	60
tctgaagtga accgcggcga caagtacatc gccaagtttc agggagaaga cacggtcgtg	120
atcgcgcca agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa	180
gtgtataatg actgtgcaaa gaagattgtt aaagatgtac ttgaaggata taatggaaca	240
atatttgcac atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat	300
gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac	360
tccatggatg aaaatttgga atttcatatt aaggtttcat attttgaaat atatttggat	420
aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac	480
cgagttccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg	540
gataccatag atgaaggaaa atccaacaga catgtagcag ttacaaatat gaatgaacat	600
agctctagga gtcacagtat atttcttatt aatgtcaaac aagagaacac acaaacggaa	660
caaaagctga gtggaaaact ttatctggtt gatttagctg gtagtgaaaa ggtagtaaa	720
actggagctg aaggtgctgt gctggatgaa gctaaaaaca tcaacaagtc actttctgct	780
cttggaatg ttatttctgc tttggctgag ggtagtacat atgttccata tcgagatagt	840
aaaatgacaa gaatccttca agattcatta ggtggcaact gtagaaccac tattgtaatt	900
tgctgctctc catcatcata caatgagtct gaaacaaaat ctacactctt atttggccaa	960
agggccaaaa caattaagaa cacagtttgt gtcaatgtgg agttaactgc agaacagtgg	1020
aaaaagaagt atgaaaaaga aaaagaaaaa aataagatcc tgcggaacac tattcagtgg	1080
cttgaaaatg agctcaacag atggcgtaat ggggagacgg tgcctattga tgaacagttt	1140
gacaaagaga aagccaactt ggaagctttc acagtggata aagatattac tcttaccaat	1200
gataaaccag caaccgcaat tggagttata ggaaatttta ctgatgctga aagaagaaag	1260
tgtgaagaag aaattgctaa attatacaaa cagcttgatg acaaggatga agaaattaac	1320
cagcaaagtc aactggtaga gaaactgaag acgcaaagt tggatcagga ggagcttttg	1380
gcatctacca gaagggatca agacaatatg caagctgagc tgaatcgctt tcaagcagaa	1440
aatgatgcct ctaaagaaga agtgaaagaa gttttacagg ccctagaaga acttgctgtc	1500
aattatgatc agaagtctca ggaagttgaa gacaaaacta aggaatatga attgcttagt	1560
gatgaattga atcagaaatc ggcaacttta gcgagtatag atgctgagct tcagaaactt	1620
aaggaaatga ccaaccacca gaaaaaacga gcagctgaga tgatggcatc ttactaaaa	1680
gaccttgacg aaataggaat tgctgtggga aataatgatg taaaggagga tccaaagtgg	1740
gaattccctc ggaagaactt gggtcttgga aaaactctag gagaaggcga atttggaaaa	1800
gtggtcaagg caacggcctt ccatctgaaa ggcagagcag ggtacaccac ggtggccgtg	1860

JPOXMLDOC01-seq1

aagatgctga aagagaacgc ctccccgagt gagctgcgag acctgctgtc agagttcaac	1920
gtcctgaagc aggtcaacca cccacatgtc atcaaattgt atggggcctg cagccaggat	1980
ggcccgtccc tcctcatcgt ggagtacgcc aaatacggct ccctgcgggg cttcctccgc	2040
gagagccgca aagtggggcc tggctacctg ggcagtggag gcagccgcaa ctccagctcc	2100
ctggaccacc cggatgagcg ggccctcacc atgggcgacc tcatctcatt tgcctggcag	2160
atctcacagg ggatgcagta tctggccgag atgaagctcg ttcacgga cttggcagcc	2220
agaaacatcc tggtagctga ggggcggaag atgaagattt cggatttcgg cttgtcccga	2280
gatgtttatg aagaggattc ctacgtgaag aggagccagg gtcggattcc agttaaatgg	2340
atggcaattg aatccctttt tgatcatatc tacaccacgc aaagtgatgt atggcttttt	2400
ggtgtcctgc tgtgggagat cgtgacccta ggggaaacc cctatcctgg gattcctcct	2460
gagcggctct tcaaccttct gaagaccggc caccggatgg agaggccaga caactgcagc	2520
gaggagatgt accgcctgat gctgcaatgc tggaagcagg agccggacaa aaggccggtg	2580
tttgcgaca tcagcaaaga cctggagaag atgatggta agaggagaga ctacttgac	2640
cttgcgcgct cactccatc tgactccctg atttatgacg acggcctctc agaggaggag	2700
acaccgctgg tggactgtaa taatgcccc ctccctcgag ccctcccttc cacatggatt	2760
gaaaacaaac tctatggtag aatttcccat gcatttacta gattctag	2808

<210> 6
 <211> 2997
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K16;R12 variant4)

<400> 6	
atggcggacc tggccgagt caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag	60
tctgaagtga accgcggcga caagtacatc gccaagtttc agggagaaga cacggctcgtg	120
atcgcgtcca agccttatgc atttgatcgg gtgttcagc caagcacatc tcaagagcaa	180
gtgtataatg actgtgcaaa gaagattgtt aaagatgtac ttgaaggata taatggaaca	240
atatttgcat atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat	300
gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac	360
tccatggatg aaaatttgga atttcatatt aaggtttcat attttgaaat atatttgat	420
aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac	480
cgagttccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg	540
gataccatag atgaaggaaa atccaacaga catgtagcag ttacaaatat gaatgaacat	600
agctctagga gtcacagtat atttcttatt aatgtcaaac aagagaacac acaaacggaa	660
caaaagctga gtggaaaact ttatctgggt gatttagctg gtagtgaaaa ggtagtaaa	720

JPOXMLDOC01-seq1

actggagctg	aaggtgctgt	gctggatgaa	gctaaaaaca	tcaacaagtc	acttttctgct	780
cttgaaatg	ttattttctgc	tttggtctgag	ggtagtacat	atgttccata	tcgagatagt	840
aaaatgacaa	gaatccttca	agattcatta	ggtggcaact	gtagaaccac	tattgtaatt	900
tgctgctctc	catcatcata	caatgagtct	gaaacaaaat	ctacactctt	at ttggccaa	960
agggccaaaa	caattaagaa	cacagtttgt	gtcaatgtgg	agttaactgc	agaacagtgg	1020
aaaaagaagt	atgaaaaaga	aaaagaaaaa	aataagatcc	tgcggaacac	tattcagtgg	1080
cttgaaatg	agctcaacag	atggcgtaat	ggggagacgg	tgcctattga	tgaacagttt	1140
gacaaagaga	aagccaactt	ggaagctttc	acagtggata	aagatattac	tcttaccaat	1200
gataaaccag	caaccgcaat	tggagttata	ggaaatttta	ctgatgctga	aagaagaaag	1260
tgtgaagaag	aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	1320
cagcaaagtc	aactggtaga	gaaactgaag	acgcaaagt	tggatcagga	ggagcttttg	1380
gcatctacca	gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	1440
aatgatgcct	ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgatk	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgcat	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgagggaaact	1740
ggcatgatag	atgaagagtt	cactgtttgca	agactctaca	ttagcaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagtttagca	gcatgtcagc	ttcgtatctc	tcaagaggat	1920
ccaaagtggg	aattccctcg	gaagaacttg	gttcttggaa	aaactctagg	agaaggcgaa	1980
tttgaaaaag	tggtcaaggc	aacggccttc	catctgaaag	gcagagcagg	gtacaccacg	2040
gtggccgtga	agatgctgaa	agagaacgcc	tccccgagt	agcttcgaga	cctgctgtca	2100
gagttcaacg	tcctgaagca	ggtcaaccac	ccacatgtca	tcaaattgta	tggggcctgc	2160
agccaggatg	gcccgtctct	cctcatcgct	gagtacgcca	aatacggctc	cctgcggggc	2220
ttcctccgct	agagccgcaa	agtggggcct	ggctacctgg	gcagtggagg	cagccgcaac	2280
tccagctccc	tggaccaccc	ggatgagcgg	gccctcacca	tgggcgacct	catctcattt	2340
gcctggcaga	tctcacagg	gatgcagtat	ctggccgaga	tgaagctcgt	tcatcgggac	2400
ttggcagcca	gaaacatcct	ggtagctgag	ggcggaaga	tgaagatttc	ggatttcggc	2460
ttgtcccgag	atgtttatga	agaggattcg	tacgtgaaga	ggagccaggg	tcggattcca	2520
gttaaatgga	tggcaattga	atcccttttt	gatcatatct	acaccacgca	aagtgatgta	2580
tggtcttttg	gtgtcctgct	gtgggagatc	gtgaccctag	ggggaaaccc	ctatcctggg	2640
attcctcctg	agcggctctt	caaccttctg	aagaccggcc	accggatgga	gaggccagac	2700
aactgcagcg	aggagatgta	ccgcctgatg	ctgcaatgct	ggaagcagga	gccggacaaa	2760

JPOXMLDOC01-seq1

aggccggtgt ttgcggacat cagcaaagac ctggagaaga tgatggttaa gaggagagac	2820
tacttgacc ttgcggcgtc cactccatct gactccctga tttatgacga cggcctctca	2880
gaggaggaga caccgctggt ggactgtaat aatgcccccc tccctcgagc cctcccttcc	2940
acatggattg aaaacaaact ctatggtaga atttcccatg catttactag attctag	2997

<210> 7
 <211> 3522
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K22;R12 variant4)

<400> 7	
atggcggacc tggccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag	60
tctgaagtga accgcggcga caagtacatc gccaaagttc agggagaaga cacggctcgtg	120
atcgcgcca agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa	180
gtgtataatg actgtgcaaa gaagattggt aaagatgtac ttgaaggata taatggaaca	240
atatttgcac atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat	300
gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac	360
tccatggatg aaaatttgga atttcataat aagggtttcat attttgaaat atatttgat	420
aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac	480
cgagttccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg	540
gataccatag atgaaggaaa atccaacaga catgtagcag ttacaaatat gaatgaacat	600
agctctagga gtcacagtat atttcttatt aatgtcaaac aagagaacac acaaacggaa	660
caaaagctga gtggaaaact ttatctgggt gatttagctg gtagtgaaaa ggtagtaaa	720
actggagctg aagggtgctgt gctggatgaa gctaaaaaca tcaacaagtc actttctgct	780
cttggaatg ttatttctgc tttggctgag ggtagtacat atgttccata tcgagatagt	840
aaaatgacaa gaatccttca agattcatta ggtggcaact gtagaaccac tattgtaatt	900
tgctgctctc catcatcata caatgagtct gaaacaaaat ctacactctt atttggccaa	960
agggccaaaa caattaagaa cacagtttgt gtcaatgtgg agttaactgc agaacagtgg	1020
aaaaagaagt atgaaaaaga aaaagaaaaa aataagatcc tgcggaacac tattcagtgg	1080
cttgaaaatg agctcaacag atggcgtaat ggggagacgg tgcctattga tgaacagttt	1140
gacaaagaga aagccaactt ggaagctttc acagtggata aagatattac tcttaccaat	1200
gataaaccag caaccgcaat tggagttata ggaaatttta ctgatgctga aagaagaaag	1260
tgtgaagaag aaattgctaa attatacaaa cagcttgatg acaaggatga agaaattaac	1320
cagcaaagtc aactggtaga gaaactgaag acgcaaagtgt tggatcagga ggagcttttg	1380
gcatctacca gaagggatca agacaatatg caagctgagc tgaatcgctt tcaagcagaa	1440

JPOXMLDOC01-seq1

aatgatgcct	ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgatc	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgag	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgaggggaact	1740
ggcatgatag	atgaagagtt	cactgttgca	agactctaca	ttagcaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagtttagca	gcatgtcagc	ttcgtatctc	tcaacatgaa	1920
gccaaaatca	agtcattgac	tgaatacctt	caaatgtgg	aacaaaagaa	aagacagttg	1980
gaggaatctg	tcgatgccct	cagtgaagaa	ctagtccagc	ttcgagcaca	agagaaagtc	2040
catgaaatgg	aaaaggagca	cttaataaag	gttcagactg	caaatgaagt	taagcaagct	2100
gttgaacagc	agatccagag	ccatagagaa	actcatcaaa	aacagatcag	tagtttgaga	2160
gatgaagtag	aagcaaaagc	aaaacttatt	actgatcttc	aagacaaaaa	ccagaaaatg	2220
atgttagagc	aggaacgtct	aagagtagaa	catgagaagt	tgaaagccac	agatcaggaa	2280
aagagcagaa	aactacatga	acttacggtt	atgcaagata	gacgagaaca	agcaagacaa	2340
gacttgaagg	gtttggaaga	gacagtggca	aaagaacttc	agactttaca	caacctgcgc	2400
aaactctttg	ttcaggacct	ggctacaaga	gttaaaaagg	aggatccaaa	gtgggaattc	2460
cctcggaga	acttggttct	tggaaaaact	ctaggagaag	gcgaatttgg	aaaagtggtc	2520
aaggcaacgg	ccttccatct	gaaaggcaga	gcagggtaca	ccacggtggc	cgtgaagatg	2580
ctgaaagaga	acgcctcccc	gagtgagctg	cgagacctgc	tgctcagagtt	caacgtcctg	2640
aagcagggtca	accaccacac	tgctcatcaaa	ttgtatgggg	cctgcagcca	ggatggccccg	2700
ctcctcctca	tcgtggagta	cgccaaatac	ggctccctgc	ggggcttcct	ccgcgagagc	2760
cgaaagtgg	ggcctggcta	cctgggcagt	ggaggcagcc	gcaactccag	ctccctggac	2820
cacccggatg	agcgggccct	caccatgggc	gacctcatct	catttgcctg	gcagatctca	2880
caggggatgc	agtatctggc	cgagatgaag	ctcgttcatc	gggacttggc	agccagaaac	2940
atcctggtag	ctgaggggcg	gaagatgaag	atttcggatt	tcggcttgtc	ccgagatggt	3000
tatgaagagg	attcctacgt	gaagaggagc	cagggtcgga	ttccagttaa	atggatggca	3060
attgaatccc	tttttgatca	tatctacacc	acgcaaagtg	atgtatggtc	ttttggtgtc	3120
ctgctgtggg	agatcgtgac	cctaggggga	aaccctatc	ctgggattcc	tcctgagcgg	3180
ctcttcaacc	ttctgaagac	cggccaccgg	atggagaggc	cagacaactg	cagcgaggag	3240
atgtaccgcc	tgatgctgca	atgctggaag	caggagccgg	acaaaaggcc	ggtgtttgcg	3300
gacatcagca	aagacctgga	gaagatgatg	gttaagagga	gagactactt	ggaccttgcg	3360
gcgtccactc	catctgactc	cctgatttat	gacgacggcc	tctcagagga	ggagacaccg	3420
ctggtggact	gtaataatgc	ccccctccct	cgagccctcc	cttcacatg	gattgaaaac	3480

JPOXMLDOC01-seq1
aaactctatg gtagaatttc ccatgcattt actagattct ag

3522

<210> 8
<211> 3627
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K23;R12 variant4)

<400> 8
atggcggacc tggccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag 60
tctgaagtga accgcggcga caagtacatc gccaaagttc agggagaaga cacggtcgtg 120
atcgcgtcca agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa 180
gtgtataatg actgtgcaaa gaagattgtt aaagatgtac ttgaaggata taatggaaca 240
atatttgc atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat 300
gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac 360
tccatggatg aaaatttggg atttcatatt aaggtttcat attttgaaat atatttggat 420
aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac 480
cgagttccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg 540
gataccatag atgaaggaaa atccaacaga catgtagcag ttacaaatat gaatgaacat 600
agctctagga gtcacagtat atttcttatt aatgtcaaac aagagaacac acaaacggaa 660
caaaagctga gtggaaaact ttatctgggt gatttagctg gtagtgaaaa ggtagtaaa 720
actggagctg aagggtgctgt gctggatgaa gctaaaaaca tcaacaagtc actttctgct 780
cttggaatg ttatttctgc tttggctgag ggtagtacat atgttccata tcgagatagt 840
aaaatgacaa gaatccttca agattcatta ggtggcaact gtagaaccac tattgtaatt 900
tgctgctctc catcatcata caatgagtct gaaacaaaat ctacactctt atttggccaa 960
agggccaaaa caattaagaa cacagtttgt gtcaatgtgg agttaactgc agaacagtgg 1020
aaaaagaagt atgaaaaaga aaaagaaaaa aataagatcc tgcggaacac tattcagtgg 1080
cttgaaaatg agctcaacag atggcgtaat ggggagacgg tgcctattga tgaacagttt 1140
gacaaagaga aagccaactt ggaagctttc acagtggata aagatattac tcttaccaat 1200
gataaaccag caaccgcaat tggagttata ggaaatttta ctgatgctga aagaagaaag 1260
tgtgaagaag aaattgctaa attatacaaa cagcttgatg acaaggatga agaaattaac 1320
cagcaaagtc aactggtaga gaaactgaag acgcaaagt tggatcagga ggagcttttg 1380
gcatctacca gaagggatca agacaatatg caagctgagc tgaatcgctt tcaagcagaa 1440
aatgatgcct ctaaagaaga agtgaaagaa gttttacagg ccctagaaga acttgctgtc 1500
aattatgata agaagtctca ggaagttgaa gacaaaacta aggaatatga attgcttagt 1560
gatgaattga atcagaaatc ggcaacttta gcgagtatag atgctgagct tcagaaactt 1620

JPOXMLDOC01-seq1

aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgag	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgaggggaact	1740
ggcatgatag	atgaagagtt	cactgttgca	agactctaca	ttagcaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagttagca	gcatgtcagc	ttcgtatctc	tcaacatgaa	1920
gccaaaatca	agtcattgac	tgaatacctt	caaaatgtgg	aacaaaagaa	aagacagttg	1980
gaggaatctg	tcgatgccct	cagtgaagaa	ctagtccagc	ttcgagcaca	agagaaagtc	2040
catgaaatgg	aaaaggagca	cttaaataag	gttcagactg	caaatgaagt	taagcaagct	2100
gttgaacagc	agatccagag	ccatagagaa	actcatcaaa	aacagatcag	tagtttgaga	2160
gatgaagtag	aagcaaaagc	aaaacttatt	actgatcttc	aagacaaaaa	ccagaaaatg	2220
atgttagagc	aggaacgtct	aagagtagaa	catgagaagt	tgaaagccac	agatcaggaa	2280
aagagcagaa	aactacatga	acttacggtt	atgcaagata	gacgagaaca	agcaagacaa	2340
gacttgaagg	gtttggaaga	gacagtggca	aaagaacttc	agactttaca	caacctgcgc	2400
aaactctttg	ttcaggacct	ggctacaaga	gttaaaaaga	gtgctgagat	tgattctgat	2460
gacaccggag	gcagcgctgc	tcagaagcaa	aaaatctcct	ttcttgaaaa	taatcttgaa	2520
cagctcacta	aagtgcacaa	acaggaggat	ccaaagtggg	aattccctcg	gaagaacttg	2580
gttcttgga	aaactctagg	agaaggcgaa	tttggaagag	tggtcaaggc	aacggccttc	2640
catctgaaag	gcagagcagg	gtacaccacg	gtggccgtga	agatgctgaa	agagaacgcc	2700
tccccgagtg	agcttcgaga	cctgctgtca	gagttcaacg	tcctgaagca	ggtcaaccac	2760
ccacatgtca	tcaaattgta	tggggcctgc	agccaggatg	gcccgtctct	cctcatcggt	2820
gagtacgcca	aatacggctc	cctgcggggc	ttcctccgcg	agagccgcaa	agtggggcct	2880
ggctacctgg	gcagtggagg	cagccgcaac	tccagctccc	tggaccaccc	ggatgagcgg	2940
gccctacca	tgggagacct	catctcattt	gcctggcaga	tctcacaggg	gatgcagtat	3000
ctggccgaga	tgaagctcgt	tcatcgggac	ttggcagcca	gaaacatcct	ggtagctgag	3060
gggcggaaga	tgaagatttc	ggatttcggc	ttgtcccgag	atgtttatga	agaggattcc	3120
tacgtgaaga	ggagccaggg	tcggattcca	gttaaatgga	tggcaattga	atcccttttt	3180
gatcatatct	acaccacgca	aagtgatgta	tggtcttttg	gtgtcctgct	gtgggagatc	3240
gtgaccctag	ggggaaaccc	ctatcctggg	attcctcctg	agcggctctt	caaccttctg	3300
aagaccggcc	accggatgga	gaggccagac	aactgcagcg	aggagatgta	ccgcctgatg	3360
ctgcaatgct	ggaagcagga	gccggacaaa	aggccggtgt	ttgcggacat	cagcaaagac	3420
ctggagaaga	tgatggttaa	gaggagagac	tacttgacc	ttgcggcgtc	cactccatct	3480
gactccctga	tttatgacga	cggcctctca	gaggaggaga	caccgctggt	ggactgtaat	3540
aatgcccccc	tccctcgagc	cctcccttcc	acatggattg	aaaacaaact	ctatggtaga	3600
atttcccatg	catttactag	attctag				3627

JPOXMLDOC01-seq1

<210> 9
 <211> 4101
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K24;R11 variant4)

<400> 9
 atggcggacc tggccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag 60
 tctgaagtga accgcggcga caagtacatc gccaagtttc agggagaaga cacggctcgtg 120
 atcgcgtcca agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa 180
 gtgtataatg actgtgcaaa gaagattgtt aaagatgtac ttgaaggata taatggaaca 240
 atatttgcag atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat 300
 gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac 360
 tccatggatg aaaatttgga atttcatatt aaggtttcat attttgaaat atatttggat 420
 aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac 480
 cgagttccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg 540
 gataccatag atgaaggaaa atccaacaga catgtagcag ttacaaatat gaatgaacat 600
 agctctagga gtcacagtat atttcttatt aatgtcaaac aagagaacac acaaacggaa 660
 caaaagctga gtggaaaact ttatctggtt gatttagctg gtagtgaaaa ggtagtaaaa 720
 actggagctg aaggtgctgt gctggatgaa gctaaaaaca tcaacaagtc actttctgct 780
 cttggaaatg ttatttctgc tttggctgag ggtagtacat atgttccata tcgagatagt 840
 aaaatgacaa gaatccttca agattcatta ggtggcaact gtagaaccac tattgtaatt 900
 tgctgctctc catcatcata caatgagtct gaaacaaaat ctacactctt atttggccaa 960
 agggccaaaa caattaagaa cacagtttgt gtcaatgtgg agttaactgc agaacagtgg 1020
 aaaaagaagt atgaaaaaga aaaagaaaaa aataagatcc tgcggaacac tattcagtgg 1080
 cttgaaaatg agctcaacag atggcgtaat ggggagacgg tgcctattga tgaacagttt 1140
 gacaaagaga aagccaactt ggaagctttc acagtggata aagatattac tcttaccaat 1200
 gataaaccag caaccgcaat tggagttata ggaaatttta ctgatgctga aagaagaaag 1260
 tgtgaagaag aaattgctaa attatacaaa cagcttgatg acaaggatga agaaattaac 1320
 cagcaaagtc aactggtaga gaaactgaag acgcaaagt tggatcagga ggagcttttg 1380
 gcatctacca gaagggatca agacaatatg caagctgagc tgaatcgctt tcaagcagaa 1440
 aatgatgcct ctaaagaaga agtgaaagaa gttttacagg ccctagaaga acttgctgtc 1500
 aattatgatc agaagtctca ggaagttgaa gacaaaacta aggaatatga attgcttagt 1560
 gatgaattga atcagaaatc ggcaacttta gcgagtatag atgctgagct tcagaaactt 1620
 aaggaaatga ccaaccacca gaaaaaacga gcagctgaga tgatggcatc ttactaaaa 1680

JPOXMLDOC01-seq1

gaccttgacag	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgaggggaact	1740
ggcatgatag	atgaagagtt	cactgttgca	agactctaca	ttagcaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagtttagca	gcatgtcagc	ttcgtatctc	tcaacatgaa	1920
gccaaaatca	agtcattgac	tgaatacctt	caaaatgtgg	aacaaaagaa	aagacagttg	1980
gaggaatctg	tcgatgccct	cagtgaagaa	ctagtccagc	ttcgagcaca	agagaaagtc	2040
catgaaatgg	aaaaggagca	cttaaataag	gttcagactg	caaatgaagt	taagcaagct	2100
gttgaacagc	agatccagag	ccatagagaa	actcatcaaa	aacagatcag	tagtttgaga	2160
gatgaagtag	aagcaaaagc	aaaactttatt	actgatcttc	aagacaaaaa	ccagaaaatg	2220
atgttagagc	aggaacgtct	aagagtagaa	catgagaagt	tgaaagccac	agatcaggaa	2280
aagagcagaa	aactacatga	acttacgggt	atgcaagata	gacgagaaca	agcaagacaa	2340
gacttgaagg	gtttggaaga	gacagtggca	aaagaacttc	agactttaca	caacctgcgc	2400
aaactctttg	ttcaggacct	ggctacaaga	gttaaaaaga	gtgctgagat	tgattctgat	2460
gacaccggag	gcagcgctgc	tcagaagcaa	aaaatctcct	ttcttgaaaa	taatcttgaa	2520
cagctcacta	aagtgcacaa	acagttggta	cgtgataatg	cagatctccg	ctgtgaactt	2580
cctaagttgg	aaaagcgact	tcgagctaca	gctgagagag	tgaaagcttt	ggaatcagca	2640
ctgaaagaag	ctaaagaaaa	tgcatctcgt	gatcgcaaac	gctatcagca	agaagtagat	2700
cgcataaagg	aagcagtcag	gtcaaagaat	atggccagaa	gagggcattc	tgcacagatt	2760
gatccactgt	gcgacgagct	gtgccgcacg	gtgatcgagc	ccgctgtcct	cttctccttc	2820
atcgtctcgg	tgctgctgtc	tgcccttctgc	atccactgct	accacaagtt	tgcccacaa	2880
ccacccatct	cctcagctga	gatgaccttc	cggaggcccg	cccaggcctt	cccggtcagc	2940
tactcctctt	ccggtgcccc	ccggccctcg	ctggactcca	tggagaacca	ggtctccgtg	3000
gatgccttca	agatcctgga	ggatccaaag	tgggaattcc	ctcggaagaa	cttggttctt	3060
ggaaaaactc	taggagaagg	cgaatttgga	aaagtgggtca	aggcaacggc	cttccatctg	3120
aaaggcagag	cagggtagac	cacgggtggc	gtgaagatgc	tgaaagagaa	cgcctccccg	3180
agtgagcttc	gagacctgct	gtcagagtgc	aacgtcctga	agcagggtcaa	ccaccacat	3240
gtcatcaa	at	tgatggggc	ctgcagccag	gatggcccgc	tcctcctcat	3300
gcaaaatag	gctccctgag	gggcttcctc	cgagagagcc	gcaaagtggg	gcctggctac	3360
ctgggcagtg	gaggcagccg	caactccagc	tccttgagcc	accggatga	gcgggccctc	3420
accatgggag	acctcatctc	atttgccctg	cagatctcac	aggggatgca	gtatctggcc	3480
gagatgaagc	tcgttcatcg	ggacttgcca	gccagaaaca	tcctggtagc	tgaggggagc	3540
aagatgaaga	tttcggattt	cggcttggtc	cgagatgttt	atgaagagga	ttcctacgtg	3600
aagaggagcc	agggctcgat	tccagttaaa	tgatgggcaa	ttgaatccct	ttttgatcat	3660
atctacacca	cgcaaagtga	tgtatgggtc	tttgggtgtc	tgctgtggga	gatcgtgacc	3720

JPOXMLDOC01-seq1

ctaggggggaa acccctatcc tgggattcct cctgagcggc tcttcaacct tctgaagacc	3780
ggccaccgga tggagaggcc agacaactgc agcgaggaga tgtaccgcct gatgctgcaa	3840
tgctggaagc aggagccgga caaaaggccg gtgtttgcgg acatcagcaa agacctggag	3900
aagatgatgg ttaagaggag agactacttg gaccttgcgg cgtccactcc atctgactcc	3960
ctgatttatg acgacggcct ctcagaggag gagacaccgc tgggtggactg taataatgcc	4020
cccctccctc gagccctccc ttccacatgg attgaaaaca aactctatgg tagaatttcc	4080
catgcattta ctagattcta g	4101

<210> 10
 <211> 2934
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K15;R12 variant2)

<400> 10	
atggcggacc tggccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag	60
tctgaagtga accgcggcga caagtacatc gccaaagttc agggagaaga cacggctcgtg	120
atcgcgtcca agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa	180
gtgtataatg actgtgcaaa gaagattgtt aaagatgtac ttgaaggata taatggaaca	240
atatttgcac atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat	300
gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac	360
tccatggatg aaaatttgga atttcatatt aagggtttcat attttgaaat atatttggat	420
aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac	480
cgagtccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg	540
gataccatag atgaaggaaa atccaacaga catgtagcag ttacaaatat gaatgaacat	600
agctctagga gtcacagtat atttcttatt aatgtcaaac aagagaacac acaaacggaa	660
caaaagctga gtgaaaaact ttatctgggt gatttagctg gtagtgaaaa ggtagtaaa	720
actggagctg aagggtgctgt gctggatgaa gctaaaaaca tcaacaagtc actttctgct	780
cttggaatg ttatttctgc tttggctgag ggtagtacat atgttccata tcgagatagt	840
aaaatgacaa gaatccttca agattcatta ggtggcaact gtagaaccac tattgtaatt	900
tgctgctctc catcatcata caatgagtct gaaacaaaat ctacactctt atttggccaa	960
agggccaaaa caattaagaa cacagtttgt gtcaatgtgg agttaactgc agaacagtgg	1020
aaaaagaagt atgaaaaaga aaaagaaaaa aataagatcc tgcggaacac tattcagtgg	1080
cttgaaaatg agctcaacag atggcgtaat ggggagacgg tgcctattga tgaacagttt	1140
gacaaagaga aagccaactt ggaagctttc acagtggata aagatattac tcttaccaat	1200
gataaaccag caaccgcaat tggagttata ggaaatttta ctgatgctga aagaagaaag	1260

JPOXMLDOC01-seq1

tgtgaagaag	aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	1320
cagcaaagtc	aactggtaga	gaaactgaag	acgcaaattg	tggatcagga	ggagcttttg	1380
gcatctacca	gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	1440
aatgatgcct	ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgatc	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgcat	aaataggaat	tgctgtggga	aataatgatg	taaaggagga	tccaaagtgg	1740
gaattccctc	ggaagaactt	ggttcttgga	aaaactctag	gagaaggcga	atttggaaaa	1800
gtggtcaagg	caacggcctt	ccatctgaaa	ggcagagcag	ggtacaccac	ggtggccgtg	1860
aagatgctga	aagagaacgc	ctccccgagt	gagctgagc	acctgctgtc	agagttcaac	1920
gtcctgaagc	aggtcaacca	cccacatgtc	atcaaattgt	atggggcctg	cagccaggat	1980
ggccccgtcc	tcctcatcgt	ggagtacgcc	aaatacggct	ccctgcgggg	cttcctccgc	2040
gagagccgca	aagtggggcc	tggttacctg	ggcagtggag	gcagccgcaa	ctccagctcc	2100
ctggaccacc	cggatgagcg	ggccctcacc	atgggagacc	tcattctcatt	tgccctggcag	2160
atctcacagg	ggatgcagta	tctggccgag	atgaagctcg	ttcatcgga	cttgccagcc	2220
agaaacatcc	tggtagctga	ggggcggaag	atgaagattt	cggatttcgg	cttggtcccga	2280
gatgtttatg	aagaggattc	ctacgtgaag	aggagccagg	gtcggattcc	agttaaattg	2340
atggcaattg	aatccctttt	tgatcatatc	tacaccacgc	aaagtgatgt	atggtctttt	2400
ggtgtcctgc	tgtgggagat	cgtgacccta	gggggaaacc	cctatcctgg	gattcctcct	2460
gagcggctct	tcaaccttct	gaagaccggc	caccggatgg	agaggccaga	caactgcagc	2520
gaggagatgt	accgcctgat	gctgcaatgc	tggaagcagg	agccggacaa	aaggccggtg	2580
tttgcgga	tcagcaaaga	cctggagaag	atgatggtta	agaggagaga	ctacttgga	2640
cttgccgctg	ccactccatc	tgactccctg	atttatgacg	acggcctctc	agaggaggag	2700
acaccgctgg	tggaactgta	taatgcccc	ctccctcgag	ccctcccttc	cacatggatt	2760
gaaaacaaac	tctatggcat	gtcagaccgg	aactggcctg	gagagagtcc	tgtaccactc	2820
acgagagctg	atggcactaa	cactgggttt	ccaagatatc	caaagtatag	tgtatatgct	2880
aactggatgc	tttcaccctc	agcggcaaaa	ttaatggaca	cgtttgatag	ttaa	2934

<210> 11
 <211> 3123
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K16;R12 variant2)

<400> 11

JPOXMLDOC01-seq1

atggcgacc	tggccgagtg	caacatcaaa	gtgatgtgtc	gcttcagacc	tctcaacgag	60
tctgaagtga	accgcggcga	caagtacatc	gccaagtttc	agggagaaga	cacggctcgtg	120
atcgcgcca	agccttatgc	atttgatcgg	gtgttccagt	caagcacatc	tcaagagcaa	180
gtgtataatg	actgtgcaaa	gaagattggt	aaagatgtac	ttgaaggata	taatggaaca	240
atatttgcac	atggacaaac	atcctctggg	aagacacaca	caatggaggg	taaacttcat	300
gatccagaag	gcatgggaat	tattccaaga	atagtgaag	atatttttaa	ttatatttac	360
tccatggatg	aaaatttgga	atttcataat	aaggtttcat	atatttgaaat	atatttggat	420
aagataaggg	acctgttaga	tgtttcaaag	accaaccttt	cagttcatga	agacaaaaac	480
cgagttccct	atgtaaaggg	gtgcacagag	cgttttgtat	gtagtcaga	tgaagttatg	540
gataccatag	atgaaggaaa	atccaacaga	catgtagcag	ttacaaatat	gaatgaacat	600
agctctagga	gtcacagtat	atttcttatt	aatgtcaaac	aagagaacac	acaaacggaa	660
caaaagctga	gtggaaaact	ttatctggtt	gatttagctg	gtagtgaaaa	ggtagtaaaa	720
actggagctg	aaggtgctgt	gctggatgaa	gctaaaaaca	tcaacaagtc	actttctgct	780
cttggaatg	ttatttctgc	tttggtgag	ggtagtacat	atgttccata	tcgagatagt	840
aaaatgacaa	gaatccttca	agattcatta	ggtggcaact	gtagaaccac	tattgtaatt	900
tgctgctctc	catcatcata	caatgagtct	gaaacaaaat	ctacactctt	atttggccaa	960
agggccaaaa	caattaagaa	cacagtttgt	gtcaatgtgg	agttaactgc	agaacagtgg	1020
aaaaagaagt	atgaaaaaga	aaaagaaaaa	aataagatcc	tgcggaacac	tattcagtgg	1080
cttgaaaatg	agctcaacag	atggcgtaat	ggggagacgg	tgccatttga	tgaacagttt	1140
gacaaagaga	aagccaactt	ggaagctttc	acagtggata	aagatattac	tcttaccaat	1200
gataaaccag	caaccgcaat	tggagttata	ggaaatttta	ctgatgctga	aagaagaaag	1260
tgtgaagaag	aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	1320
cagcaaagtc	aactggtaga	gaaactgaag	acgcaaagt	tggatcagga	ggagcttttg	1380
gcatctacca	gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	1440
aatgatgcct	ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgatc	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgcat	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgagggaact	1740
ggcatgatag	atgaagagtt	cactgttgca	agactctaca	ttagcaaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagtttagca	gcatgtcagc	ttcgtatctc	tcaagaggat	1920
ccaaagtggg	aattccctcg	gaagaacttg	gttcttgga	aaactctagg	agaaggcgaa	1980
tttgaaaaag	tggtcaaggc	aacggccttc	catctgaaag	gcagagcagg	gtacaccacg	2040

JPOXMLDOC01-seq1

gtggccgtga	agatgctgaa	agagaacgcc	tccccgagtg	agcttcgaga	cctgctgtca	2100
gagttcaacg	tcctgaagca	ggtcaaccac	ccacatgtca	tcaaattgta	tggggcctgc	2160
agccaggatg	gcccgtctct	cctcatcgtg	gagtacgcca	aatacggctc	cctgcggggc	2220
ttcctccgcg	agagccgcaa	agtggggcct	ggctacctgg	gcagtggagg	cagccgcaac	2280
tccagctccc	tggaccaccc	ggatgagcgg	gccctcacca	tgggcgacct	catctcattt	2340
gcctggcaga	tctcacaggg	gatgcagtat	ctggccgaga	tgaagctcgt	tcacggggac	2400
ttggcagcca	gaaacatcct	ggtagctgag	gggcggaaga	tgaagatttc	ggatttcggc	2460
ttgtcccag	atgtttatga	agaggattcg	tacgtgaaga	ggagccaggg	tcggattcca	2520
gttaaattgga	tggcaattga	atcccttttt	gatcatatct	acaccacgca	aagtgatgta	2580
tggctctttt	gtgtcctgct	gtgggagatc	gtgaccctag	ggggaaacct	ctatcctggg	2640
attcctcctg	agcggctctt	caaccttctg	aagaccggcc	accggatgga	gaggccagac	2700
aactgcagcg	aggagatgta	ccgcctgatg	ctgcaatgct	ggaagcagga	gccggacaaa	2760
aggccggtgt	ttgcggacat	cagcaaagac	ctggagaaga	tgatggttaa	gaggagagac	2820
tacttggacc	ttgcggcgct	cactccatct	gactccctga	tttatgacga	cggcctctca	2880
gaggaggaga	caccgctggt	ggactgtaat	aatgcccccc	tccctcgagc	cctcccttcc	2940
acatggattg	aaaacaaact	ctatggcatg	tcagaccgca	actggcctgg	agagagtcct	3000
gtaccactca	cgagagctga	tggcactaac	actgggtttc	caagatatcc	aaatgatagt	3060
gtatatgcta	actggatgct	ttcacccctca	gcggcaaaat	taatggacac	gtttgatagt	3120
taa						3123

<210> 12
 <211> 3648
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K22;R12 variant2)

<400> 12	
atggcggacc	60
tggccgagtg	
caacatcaaa	
gtgatgtgtc	
gcttcagacc	
tctcaacgag	
tctgaagtga	120
accgcggcga	
caagtacatc	
gccaagtttc	
agggagaaga	
cacggctcgtg	
atcgcgtcca	180
agccttatgc	
atttgatcgg	
gtgttccagt	
caagcacatc	
tcaagagcaa	
gtgtataatg	240
actgtgcaaa	
gaagattgtt	
aaagatgtac	
ttgaaggata	
taatggaaca	
atatttgcac	300
atggacaaac	
atcctctggg	
aagacacaca	
caatggaggg	
taaacttcat	
gatccagaag	360
gcatgggaat	
tattccaaga	
atagtgaag	
atatttttaa	
ttatatttac	
tccatggatg	420
aaaatttgga	
atttcatatt	
aaggtttcat	
atatttgaaat	
atatttggat	
aagataaggg	480
acctgttaga	
tgtttcaaag	
accaaccttt	
cagttcatga	
agacaaaaac	
cgagttccct	540
atgtaaaggg	
gtgcacagag	
cgttttgtat	
gtagtccaga	
tgaagttatg	

JPOXMLDOC01-seq1

gataccatag	atgaaggaaa	atccaacaga	catgtagcag	ttacaaatat	gaatgaacat	600
agctctagga	gtcacagtat	atttcttatt	aatgtcaaac	aagagaacac	acaaacggaa	660
caaaagctga	gtggaaaact	ttatctgggt	gatttagctg	gtagtgaaaa	ggttagtaaa	720
actggagctg	aaggtgctgt	gctggatgaa	gctaaaaaca	tcaacaagtc	actttctgct	780
cttggaaatg	ttatttctgc	tttggtgag	ggtagtacat	atgttccata	tcgagatagt	840
aaaatgacaa	gaatccttca	agattcatta	ggtaggcaact	gtagaaccac	tattgtaatt	900
tgctgctctc	catcatcata	caatgagtct	gaaacaaaat	ctacactctt	atttggccaa	960
agggccaaaa	caattaagaa	cacagtttgt	gtcaatgtgg	agttaactgc	agaacagtgg	1020
aaaaagaagt	atgaaaaaga	aaaagaaaaa	aataagatcc	tgcggaacac	tattcagtgg	1080
cttgaaaatg	agctcaacag	atggcgtaat	ggggagacgg	tgcctattga	tgaacagttt	1140
gacaaagaga	aagccaactt	ggaagctttc	acagtggata	aagatattac	tcttaccaat	1200
gataaaccag	caaccgcaat	tggagttata	ggaaatttta	ctgatgctga	aagaagaaag	1260
tgtgaagaag	aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	1320
cagcaaagtc	aactggtaga	gaaactgaag	acgcaaattg	tggatcagga	ggagcttttg	1380
gcatctacca	gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	1440
aatgatgcct	ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgata	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgcat	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgaggggaact	1740
ggcatgatag	atgaagagtt	cactgttgca	agactctaca	ttagcaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagtttagca	gcatgtcagc	ttcgtatctc	tcaacatgaa	1920
gccaaaatca	agtcattgac	tgaatacctt	caaaatgtgg	aacaaaagaa	aagacagttg	1980
gaggaatctg	tcgatgccct	cagtgaagaa	ctagtccagc	ttcgagcaca	agagaaagtc	2040
catgaaatgg	aaaaggagca	cttaaataag	gttcagactg	caaatgaagt	taagcaagct	2100
gttgaacagc	agatccagag	ccatagagaa	actcatcaaa	aacagatcag	tagtttgaga	2160
gatgaagtag	aagcaaaagc	aaaacttatt	actgatcttc	aagacaaaaa	ccagaaaatg	2220
atgtagagc	aggaacgtct	aagagtagaa	catgagaagt	tgaagccac	agatcaggaa	2280
aagagcagaa	aactacatga	acttacggtt	atgcaagata	gacgagaaca	agcaagacaa	2340
gacttgaagg	gtttggaaga	gacagtggca	aaagaacttc	agactttaca	caacctgcgc	2400
aaactctttg	ttcaggacct	ggctacaaga	gttaaaaagg	aggatccaaa	gtgggaattc	2460
cctcgggaaga	acttggttct	tggaaaaact	ctaggagaag	gcgaatttgg	aaaagtggtc	2520
aaggcaacgg	ccttccatct	gaaaggcaga	gcagggtaca	ccacggtggc	cgtgaagatg	2580

JPOXMLDOC01-seq1

ctgaaagaga	acgcctcccc	gagtgagctg	cgagacctgc	tgtcagagtt	caacgtcctg	2640
aagcagggtca	accacccaca	tgtcatcaaa	ttgtatgggg	cctgcagcca	ggatggccccg	2700
ctcctcctca	tcgtggagta	cgccaaatac	ggctccctgc	ggggcttcct	ccgcgagagc	2760
cgcaaagtgg	ggcctggcta	cctgggcagt	ggaggcagcc	gcaactccag	ctccctggac	2820
cacccggatg	agcggggcct	caccatgggc	gacctcatct	catttgcctg	gcagatctca	2880
caggggatgc	agtatctggc	cgagatgaag	ctcgttcatc	gggacttggc	agccagaaac	2940
atcctggtag	ctgaggggcg	gaagatgaag	atttcggatt	tcggcttgtc	ccgagatggt	3000
tatgaagagg	attcctacgt	gaagaggagc	cagggtcgga	ttccagttaa	atggatggca	3060
attgaatccc	tttttgatca	tatctacacc	acgcaaagtg	atgtatggtc	ttttggtgtc	3120
ctgctgtggg	agatcgtgac	cctaggggga	aaccctatc	ctgggattcc	tcctgagcgg	3180
ctcttcaacc	ttctgaagac	cggccaccgg	atggagaggc	cagacaactg	cagcgaggag	3240
atgtaccgcc	tgatgctgca	atgctggaag	caggagccgg	acaaaaggcc	ggtgtttgcg	3300
gacatcagca	aagacctgga	gaagatgatg	gttaagagga	gagactactt	ggaccttgcg	3360
gcgctcactc	catctgactc	cctgatttat	gacgacggcc	tctcagagga	ggagacaccg	3420
ctggtggact	gtaataatgc	ccccctccct	cgagccctcc	cttcacatg	gattgaaaac	3480
aaactctatg	gcatgtcaga	cccgaactgg	cctggagaga	gtcctgtacc	actcacgaga	3540
gctgatggca	ctaactctgg	gtttccaaga	tatccaaatg	atagtgtata	tgctaactgg	3600
atgctttcac	cctcagcggc	aaaattaatg	gacacgtttg	atagttaa		3648

<210> 13
 <211> 3753
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K23;R12 variant2)

<400> 13	
atggcggacc	60
tggccgagtg	
caacatcaaa	
gtgatgtgtc	
gcttcagacc	
tctcaacgag	
tctgaagtga	120
accgcggcga	
caagtacatc	
gccaaagttc	
agggagaaga	
cacggctcgtg	
atcgcgcca	180
agccttatgc	
atttgatcgg	
gtgttccagt	
caagcacatc	
tcaagagcaa	
gtgtataatg	240
actgtgcaaa	
gaagattggt	
aaagatgtac	
ttgaaggata	
taatggaaca	
atatttgc	300
atggacaaac	
atcctctggg	
aagacacaca	
caatggaggg	
taaacttcat	
gatccagaag	360
gcatgggaat	
tattccaaga	
atagtgaag	
atatttttaa	
ttatatttac	
tccatggatg	420
aaaatttgga	
atttcatatt	
aaggtttcat	
atatttgaaat	
atatttggat	
aagataaggg	480
acctgttaga	
tgtttcaaag	
accaaccttt	
cagttcatga	
agacaaaaac	
cgagttccct	540
atgtaaaggg	
gtgcacagag	
cgttttgtat	
gtagtccaga	
tgaagttatg	
gataccatag	600
atgaaggaaa	
atccaacaga	
catgtagcag	
ttacaaatat	
gaatgaacat	

JPOXMLDOC01-seq1

agctctagga	gtcacagtat	atttcttatt	aatgtcaaac	aagagaacac	acaaacggaa	660
caaaagctga	gtggaaaact	ttatctgggt	gatttagctg	gtagtgaaaa	ggttagtaaa	720
actggagctg	aaggtgctgt	gctggatgaa	gctaaaaaca	tcaacaagtc	actttctgct	780
cttggaatg	ttatttctgc	tttggctgag	ggtagtacat	atgttccata	tcgagatagt	840
aaaatgacaa	gaatccttca	agattcatta	ggtggcaact	gtagaaccac	tattgtaatt	900
tgctgctctc	catcatcata	caatgagtct	gaaacaaaat	ctacactctt	atttggccaa	960
agggccaaaa	caattaagaa	cacagtttgt	gtcaatgtgg	agttaactgc	agaacagtgg	1020
aaaaagaagt	atgaaaaaga	aaaagaaaaa	aataagatcc	tgcggaacac	tattcagtgg	1080
cttgaaaatg	agctcaacag	atggcgtaat	ggggagacgg	tgccatttga	tgaacagttt	1140
gacaaagaga	aagccaactt	ggaagctttc	acagtggata	aagatattac	tcttaccaat	1200
gataaaccag	caaccgcaat	tggagttata	ggaaatttta	ctgatgctga	aagaagaaag	1260
tgtgaagaag	aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	1320
cagcaaagtc	aactggtaga	gaaactgaag	acgcaaagt	tggatcagga	ggagcttttg	1380
gcatctacca	gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	1440
aatgatgcct	ctaaagaaga	agtgaaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgatc	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgcat	aaataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgagggaaact	1740
ggcatgatag	atgaagagtt	cactgttgca	agactctaca	ttagcaaaat	gaagtcagaa	1800
gtaaaaacca	tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	1860
aaaatggaag	aaaatgaaaa	ggagtttagca	gcatgtcagc	ttcgtatctc	tcaacatgaa	1920
gccaaaatca	agtcattgac	tgaatacctt	caaatgtgg	aacaaaagaa	aagacagttg	1980
gaggaatctg	tcgatgccct	cagtgaagaa	ctagtccagc	ttcgagcaca	agagaaagtc	2040
catgaaatgg	aaaaggagca	cttaaataag	gttcagactg	caaatgaagt	taagcaagct	2100
gttgaacagc	agatccagag	ccatagagaa	actcatcaaa	aacagatcag	tagtttgaga	2160
gatgaagtag	aagcaaaagc	aaaacttatt	actgatcttc	aagacaaaaa	ccagaaaatg	2220
atgtagagc	aggaacgtct	aagagtagaa	catgagaagt	tgaaagccac	agatcaggaa	2280
aagagcagaa	aactacatga	acttacggtt	atgcaagata	gacgagaaca	agcaagacaa	2340
gacttgaagg	gtttggaaga	gacagtggca	aaagaacttc	agactttaca	caacctgcgc	2400
aaactctttg	ttcaggacct	ggctacaaga	gttaaaaaga	gtgctgagat	tgattctgat	2460
gacaccggag	gcagcgctgc	tcagaagcaa	aaaatctcct	ttcttgaaaa	taatcttgaa	2520
cagctcacta	aagtgcacaa	acaggaggat	ccaaagtggg	aattccctcg	gaagaacttg	2580
gttcttgga	aaactctagg	agaaggcgaa	tttggaagaa	tggtcaaggc	aacggccttc	2640

JPOXMLDOC01-seq1

catctgaaag gcagagcagg gtacaccacg gtggccgtga agatgctgaa agagaacgcc	2700
tccccgagtg agcttcgaga cctgctgtca gagttcaacg tcctgaagca ggtcaaccac	2760
ccacatgtca tcaaattgta tggggcctgc agccaggatg gcccgctcct cctcatcgtg	2820
gagtacgcca aatacggctc cctgcggggc ttcctccgcg agagccgcaa agtggggcct	2880
ggctacctgg gcagtggagg cagccgcaac tccagctccc tggaccaccc ggatgagcgg	2940
gccctacca tgggcgacct catctcattt gcctggcaga tctcacaggg gatgcagtat	3000
ctggccgaga tgaagctcgt tcatcgggac ttggcagcca gaaacatcct ggtagctgag	3060
gggcggaaga tgaagatttc ggatttcggc ttgtcccagag atgtttatga agaggattcc	3120
tacgtgaaga ggagccaggg tcggattcca gttaaattgga tggcaattga atcccttttt	3180
gatcatatct acaccacgca aagtgatgta tggctctttt gtgtcctgct gtgggagatc	3240
gtgaccctag ggggaaaccc ctatcctggg attcctcctg agcggctctt caaccttctg	3300
aagaccggcc accggatgga gaggccagac aactgcagcg aggagatgta ccgcctgatg	3360
ctgcaatgct ggaagcagga gccggacaaa aggccggtgt ttgcggacat cagcaaagac	3420
ctggagaaga tgatgggttaa gaggagagac tacttggacc ttgcggcgtc cactccatct	3480
gactccctga tttatgacga cggcctctca gaggaggaga caccgctggt ggactgtaat	3540
aatgcccccc tccctcgagc cctcccttcc acatggattg aaaacaaact ctatggcatg	3600
tcagaccgga actggcctgg agagagtcct gtaccactca cgagagctga tggcactaac	3660
actgggtttc caagatatcc aaatgatagt gtatatgcta actggatgct ttcaccctca	3720
gcggcaaaat taatggacac gtttgatagt taa	3753

<210> 14
 <211> 2958
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K15;R11 variant4)

<400> 14	
atggcggacc tggccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag	60
tctgaagtga accgcggcga caagtacatc gccaagtttc agggagaaga cacggtcgtg	120
atcgcgtcca agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa	180
gtgtataatg actgtgcaaa gaagattgtt aaagatgtac ttgaaggata taatggaaca	240
atatttgcat atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat	300
gatccagaag gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac	360
tccatggatg aaaatttgga atttcatatt aaggtttcat attttgaaat atatttgat	420
aagataaggg acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac	480
cgagttccct atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg	540

JPOXMLDOC01-seq1

gataccatag	atgaaggaaa	atccaacaga	catgtagcag	ttacaaatat	gaatgaacat	600
agctctagga	gtcacagtat	atttcttatt	aatgtcaaac	aagagaacac	acaaacggaa	660
caaaagctga	gtggaaaact	ttatctgggt	gatttagctg	gtagtgaaaa	ggttagtaaa	720
actggagctg	aaggtgctgt	gctggatgaa	gctaaaaaca	tcaacaagtc	actttctgct	780
cttggaatg	ttatttctgc	tttggtgag	ggtagtacat	atgttccata	tcgagatagt	840
aaaatgacaa	gaatccttca	agattcatta	ggtaggcaact	gtagaaccac	tattgtaatt	900
tgctgctctc	catcatcata	caatgagtct	gaaacaaaat	ctacactctt	atttggccaa	960
agggccaaaa	caattaagaa	cacagtttgt	gtcaatgtgg	agttaactgc	agaacagtgg	1020
aaaaagaagt	atgaaaaaga	aaaagaaaaa	aataagatcc	tgcggaacac	tattcagtgg	1080
cttgaaaatg	agctcaacag	atggcgtaat	ggggagacgg	tgcctattga	tgaacagttt	1140
gacaaagaga	aagccaactt	ggaagctttc	acagtggata	aagatattac	tcttaccaat	1200
gataaaccag	caaccgcaat	tggagttata	ggaaatttta	ctgatgctga	aagaagaaag	1260
tgtgaagaag	aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	1320
cagcaaagtc	aactggtaga	gaaactgaag	acgcaaattg	tggatcagga	ggagcttttg	1380
gcatctacca	gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	1440
aatgatgcct	ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	1500
aattatgata	agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	1560
gatgaattga	atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaactt	1620
aaggaaatga	ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	1680
gaccttgcat	aaataggaat	tgctgtggga	aataatgatg	taaagtttgc	ccacaagcca	1740
cccatctcct	cagctgagat	gaccttccgg	aggcccgcgc	aggccttccc	ggtcagctac	1800
tcctcttccg	gtgcccgcgc	gccctcgctg	gactccatgg	agaaccaggt	ctccgtggat	1860
gccttcaaga	tcctggagga	tccaaagtgg	gaattccctc	ggaagaactt	ggttcttgga	1920
aaaactctag	gagaaggcga	atttggaaaa	gtggtcaagg	caacggcctt	ccatctgaaa	1980
ggcagagcag	ggtacaccac	ggtggccgtg	aagatgctga	aagagaacgc	ctccccgagt	2040
gagctgagag	acctgctgtc	agagttcaac	gtcctgaagc	aggtcaacca	cccacatgtc	2100
atcaaattgt	atggggcctg	cagccaggat	ggcccgtctc	tcctcatcgt	ggagtacgcc	2160
aaatacggct	ccctgcgggg	cttcctccgc	gagagccgca	aagtggggcc	tggctacctg	2220
ggcagtgag	gcagccgcaa	ctccagctcc	ctggaccacc	cggatgagcg	ggccctcacc	2280
atgggcgacc	tcattctcatt	tgcttgagag	atctcacagg	ggatgcagta	tctggccgag	2340
atgaagctcg	ttcatcgga	cttggcagcc	agaaacatcc	tggtagctga	ggggcggaag	2400
atgaagattt	cggatttcgg	cttggtccga	gatgtttatg	aagaggattc	ctacgtgaag	2460
aggagccagg	gtcggattcc	agttaaatgg	atggcaattg	aatccctttt	tgatcatatc	2520
tacaccacgc	aaagtgatgt	atggtctttt	ggtgtcctgc	tgtgggagat	cgtgacccta	2580

JPOXMLDOC01-seq1

gggggaaacc cctatcctgg gattcctcct gagcggctct tcaaccttct gaagaccggc 2640
caccggatgg agaggccaga caactgcagc gaggagatgt accgcctgat gctgcaatgc 2700
tggaagcagg agccggacaa aaggccggtg tttgcggaca tcagcaaaga cctggagaag 2760
atgatggtta agaggagaga ctacttggac cttgcggcgt ccactccatc tgactccctg 2820
atttatgacg acggcctctc agaggaggag acaccgctgg tggactgtaa taatgcccc 2880
ctccctcgag ccctcccttc cacatggatt gaaaacaaac tctatggtag aatttcccat 2940
gcatttacta gattctag 2958

<210> 15
<211> 935
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K15;R12 variant 4)

<400> 15

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro

JPOXMLDOC01-seq1

165

170

175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
 180 185 190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
 195 200 205

Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
 210 215 220

Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
 225 230 235 240

Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
 245 250 255

Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
 260 265 270

Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
 275 280 285

Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro
 290 295 300

Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
 305 310 315 320

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

Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
 340 345 350

Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
 355 360 365

Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
 370 375 380

Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
 385 390 395 400

Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
 405 410 415

Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 420 425 430

Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 Page 34

JPOXMLDOC01-seq1

435

440

445

Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
 450 455 460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
 465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
 485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
 500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
 515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
 530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
 545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Glu
 565 570 575

Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr
 580 585 590

Leu Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe His
 595 600 605

Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys
 610 615 620

Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn
 625 630 635 640

Val Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala
 645 650 655

Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr
 660 665 670

Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly
 675 680 685

Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro
 690 695 700

Asp Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln
 Page 35

JPOXMLDOC01-seq1

705 710 715 720

Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg
 725 730 735

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

Ile Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr
 755 760 765

Val Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu
 770 775 780

Ser Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe
 785 790 795 800

Gly Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr Pro
 805 810 815

Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly His Arg
 820 825 830

Met Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu Met Leu
 835 840 845

Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala Asp Ile
 850 855 860

Ser Lys Asp Leu Glu Lys Met Met Val Lys Arg Arg Asp Tyr Leu Asp
 865 870 875 880

Leu Ala Ala Ser Thr Pro Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu
 885 890 895

Ser Glu Glu Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro
 900 905 910

Arg Ala Leu Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Arg Ile
 915 920 925

Ser His Ala Phe Thr Arg Phe
 930 935

<210> 16
 <211> 998
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K16;R12 variant4)

JPOXMLDOC01-seq1

<400> 16

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
165 170 175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
180 185 190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
195 200 205

Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
210 215 220

Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
225 230 235 240

Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
245 250 255

Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
Page 37

JPOXMLDOC01-seq1

260

265

270

Thr Tyr Val₂₇₅ Pro Tyr Arg Asp Ser₂₈₀ Lys Met Thr Arg Ile₂₈₅ Leu Gln Asp
 Ser Leu₂₉₀ Gly Gly Asn Cys Arg₂₉₅ Thr Thr Ile Val Ile₃₀₀ Cys Cys Ser Pro
 Ser₃₀₅ Ser Tyr Asn Glu Ser₃₁₀ Glu Thr Lys Ser Thr₃₁₅ Leu Leu Phe Gly Gln₃₂₀
 Arg Ala Lys Thr Ile₃₂₅ Lys Asn Thr Val Cys₃₃₀ Val Asn Val Glu Leu₃₃₅ Thr
 Ala Glu Gln Trp₃₄₀ Lys Lys Lys Tyr Glu₃₄₅ Lys Glu Lys Glu Lys₃₅₀ Asn Lys
 Ile Leu Arg₃₅₅ Asn Thr Ile Gln Trp₃₆₀ Leu Glu Asn Glu Leu₃₆₅ Asn Arg Trp
 Arg Asn₃₇₀ Gly Glu Thr Val Pro₃₇₅ Ile Asp Glu Gln Phe₃₈₀ Asp Lys Glu Lys
 Ala₃₈₅ Asn Leu Glu Ala Phe₃₉₀ Thr Val Asp Lys Asp₃₉₅ Ile Thr Leu Thr Asn₄₀₀
 Asp Lys Pro Ala Thr₄₀₅ Ala Ile Gly Val Ile₄₁₀ Gly Asn Phe Thr Asp₄₁₅ Ala
 Glu Arg Arg Lys₄₂₀ Cys Glu Glu Glu Ile₄₂₅ Ala Lys Leu Tyr Lys₄₃₀ Gln Leu
 Asp Asp Lys₄₃₅ Asp Glu Glu Ile Asn₄₄₀ Gln Gln Ser Gln Leu₄₄₅ Val Glu Lys
 Leu Lys₄₅₀ Thr Gln Met Leu Asp₄₅₅ Gln Glu Glu Leu Leu₄₆₀ Ala Ser Thr Arg
 Arg₄₆₅ Asp Gln Asp Asn Met₄₇₀ Gln Ala Glu Leu Asn₄₇₅ Arg Leu Gln Ala Glu₄₈₀
 Asn Asp Ala Ser Lys₄₈₅ Glu Glu Val Lys Glu₄₉₀ Val Leu Gln Ala Leu₄₉₅ Glu
 Glu Leu Ala Val₅₀₀ Asn Tyr Asp Gln Lys₅₀₅ Ser Gln Glu Val Glu₅₁₀ Asp Lys
 Thr Lys Glu₅₁₅ Tyr Glu Leu Leu Ser₅₂₀ Asp Glu Leu Asn Gln₅₂₅ Lys Ser Ala
 Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr

JPOXMLDOC01-seq1

530

535

540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
565 570 575

Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
580 585 590

Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
595 600 605

Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
610 615 620

Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln Glu Asp
625 630 635 640

Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr Leu
645 650 655

Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe His Leu
660 665 670

Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys Glu
675 680 685

Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn Val
690 695 700

Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala Cys
705 710 715 720

Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly
725 730 735

Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr
740 745 750

Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro Asp
755 760 765

Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile
770 775 780

Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg Asp
785 790 795 800

Leu Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys Met Lys Ile

JPOXMLDOC01-seq1

805

810

815

Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val
820 825 830

Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu Ser
835 840 845

Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe Gly
850 855 860

Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr Pro Gly
865 870 875 880

Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly His Arg Met
885 890 895

Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu Met Leu Gln
900 905 910

Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala Asp Ile Ser
915 920 925

Lys Asp Leu Glu Lys Met Met Val Lys Arg Arg Asp Tyr Leu Asp Leu
930 935 940

Ala Ala Ser Thr Pro Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu Ser
945 950 955 960

Glu Glu Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg
965 970 975

Ala Leu Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Arg Ile Ser
980 985 990

His Ala Phe Thr Arg Phe
995

<210> 17
<211> 1173
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K22;R12 variant4)

<400> 17

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
Page 40

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
 35 40 45
 Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
 50 55 60
 Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
 65 70 75 80
 Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
 85 90 95
 Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
 100 105 110
 Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
 115 120 125
 His Ile Lys Val Ser Tyr Phe Glu Ile Tyr Leu Asp Lys Ile Arg Asp
 130 135 140
 Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
 145 150 155 160
 Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
 165 170 175
 Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
 180 185 190
 Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
 195 200 205
 Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
 210 215 220
 Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
 225 230 235 240
 Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
 245 250 255
 Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
 260 265 270
 Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
 275 280 285
 Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro

JPOXMLDOC01-seq1

290

295

300

Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
 305 310 315 320

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

Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
 340 345 350

Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
 355 360 365

Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
 370 375 380

Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
 385 390 395 400

Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
 405 410 415

Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 420 425 430

Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 435 440 445

Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
 450 455 460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
 465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
 485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
 500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
 515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
 530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
 545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln

835

840

845

Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys Glu Asn
850 855 860

Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn Val Leu
865 870 875 880

Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala Cys Ser
885 890 895

Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly Ser
900 905 910

Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr Leu
915 920 925

Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro Asp Glu
930 935 940

Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile Ser
945 950 955 960

Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg Asp Leu
965 970 975

Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys Met Lys Ile Ser
980 985 990

Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val Lys
995 1000 1005

Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu Ser
1010 1015 1020

Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe
1025 1030 1035

Gly Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr
1040 1045 1050

Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly
1055 1060 1065

His Arg Met Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg
1070 1075 1080

Leu Met Leu Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val
1085 1090 1095

Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys Met Met Val Lys Arg
Page 44

JPOXMLDOC01-seq1

1100

1105

1110

Arg Asp Tyr Leu Asp Leu Ala Ala Ser Thr Pro Ser Asp Ser Leu
1115 1120 1125

Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu Thr Pro Leu Val Asp
1130 1135 1140

Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu Pro Ser Thr Trp Ile
1145 1150 1155

Glu Asn Lys Leu Tyr Gly Arg Ile Ser His Ala Phe Thr Arg Phe
1160 1165 1170

<210> 18
<211> 1208
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K23;R12 variant4)

<400> 18

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn

JPOXMLDOC01-seq1

145 150 155 160
 Arg Val Pro Tyr Val₁₆₅ Lys Gly Cys Thr Glu₁₇₀ Arg Phe Val Cys Ser₁₇₅ Pro
 Asp Glu Val Met₁₈₀ Asp Thr Ile Asp Glu₁₈₅ Gly Lys Ser Asn Arg₁₉₀ His Val
 Ala Val Thr₁₉₅ Asn Met Asn Glu His₂₀₀ Ser Ser Arg Ser His₂₀₅ Ser Ile Phe
 Leu Ile₂₁₀ Asn Val Lys Gln Glu₂₁₅ Asn Thr Gln Thr Glu₂₂₀ Gln Lys Leu Ser
 Gly₂₂₅ Lys Leu Tyr Leu Val₂₃₀ Asp Leu Ala Gly Ser₂₃₅ Glu Lys Val Ser Lys₂₄₀
 Thr Gly Ala Glu Gly₂₄₅ Ala Val Leu Asp Glu₂₅₀ Ala Lys Asn Ile Asn₂₅₅ Lys
 Ser Leu Ser Ala₂₆₀ Leu Gly Asn Val Ile₂₆₅ Ser Ala Leu Ala Glu₂₇₀ Gly Ser
 Thr Tyr Val₂₇₅ Pro Tyr Arg Asp Ser₂₈₀ Lys Met Thr Arg Ile₂₈₅ Leu Gln Asp
 Ser Leu₂₉₀ Gly Gly Asn Cys Arg₂₉₅ Thr Thr Ile Val Ile₃₀₀ Cys Cys Ser Pro
 Ser₃₀₅ Ser Tyr Asn Glu Ser₃₁₀ Glu Thr Lys Ser Thr₃₁₅ Leu Leu Phe Gly Gln₃₂₀
 Arg Ala Lys Thr Ile₃₂₅ Lys Asn Thr Val Cys₃₃₀ Val Asn Val Glu Leu₃₃₅ Thr
 Ala Glu Gln Trp₃₄₀ Lys Lys Lys Tyr Glu₃₄₅ Lys Glu Lys Glu Lys₃₅₀ Asn Lys
 Ile Leu Arg₃₅₅ Asn Thr Ile Gln Trp₃₆₀ Leu Glu Asn Glu Leu₃₆₅ Asn Arg Trp
 Arg Asn₃₇₀ Gly Glu Thr Val Pro₃₇₅ Ile Asp Glu Gln Phe₃₈₀ Asp Lys Glu Lys
 Ala₃₈₅ Asn Leu Glu Ala Phe₃₉₀ Thr Val Asp Lys Asp₃₉₅ Ile Thr Leu Thr Asn₄₀₀
 Asp Lys Pro Ala Thr₄₀₅ Ala Ile Gly Val Ile₄₁₀ Gly Asn Phe Thr Asp₄₁₅ Ala
 Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 Page 46

JPOXMLDOC01-seq1

420

425

430

Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
435 440 445

Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
450 455 460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
565 570 575

Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
580 585 590

Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
595 600 605

Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
610 615 620

Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln His Glu
625 630 635 640

Ala Lys Ile Lys Ser Leu Thr Glu Tyr Leu Gln Asn Val Glu Gln Lys
645 650 655

Lys Arg Gln Leu Glu Glu Ser Val Asp Ala Leu Ser Glu Glu Leu Val
660 665 670

Gln Leu Arg Ala Gln Glu Lys Val His Glu Met Glu Lys Glu His Leu
675 680 685

Asn Lys Val Gln Thr Ala Asn Glu Val Lys Gln Ala Val Glu Gln Gln
Page 47

690

695

Ile Gln Ser His Arg Glu Thr His Gln Lys Gln Ile Ser Ser Leu Arg
705 710 715 720

Asp Glu Val Glu Ala Lys Ala Lys Leu Ile Thr Asp Leu Gln Asp Gln
725 730 735

Asn Gln Lys Met Met Leu Glu Gln Glu Arg Leu Arg Val Glu His Glu
740 745 750

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

Thr Val Met Gln Asp Arg Arg Glu Gln Ala Arg Gln Asp Leu Lys Gly
770 775 780

Leu Glu Glu Thr Val Ala Lys Glu Leu Gln Thr Leu His Asn Leu Arg
785 790 795 800

Lys Leu Phe Val Gln Asp Leu Ala Thr Arg Val Lys Lys Ser Ala Glu
805 810 815

Ile Asp Ser Asp Asp Thr Gly Gly Ser Ala Ala Gln Lys Gln Lys Ile
820 825 830

Ser Phe Leu Glu Asn Asn Leu Glu Gln Leu Thr Lys Val His Lys Gln
835 840 845

Glu Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys
850 855 860

Thr Leu Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe
865 870 875 880

His Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu
885 890 895

Lys Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe
900 905 910

Asn Val Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly
915 920 925

Ala Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys
930 935 940

Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro
945 950 955 960

Gly Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His

Pro Asp Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp
 980 985 990

Gln Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His
 995 1000 1005

Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys
 1010 1015 1020

Met Lys Ile Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu
 1025 1030 1035

Asp Ser Tyr Val Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp
 1040 1045 1050

Met Ala Ile Glu Ser Leu Phe Asp His Ile Tyr Thr Thr Gln Ser
 1055 1060 1065

Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Val Thr Leu
 1070 1075 1080

Gly Gly Asn Pro Tyr Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn
 1085 1090 1095

Leu Leu Lys Thr Gly His Arg Met Glu Arg Pro Asp Asn Cys Ser
 1100 1105 1110

Glu Glu Met Tyr Arg Leu Met Leu Gln Cys Trp Lys Gln Glu Pro
 1115 1120 1125

Asp Lys Arg Pro Val Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys
 1130 1135 1140

Met Met Val Lys Arg Arg Asp Tyr Leu Asp Leu Ala Ala Ser Thr
 1145 1150 1155

Pro Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu
 1160 1165 1170

Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu
 1175 1180 1185

Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Arg Ile Ser His
 1190 1195 1200

Ala Phe Thr Arg Phe
 1205

<210> 19

JPOXMLDOC01-seq1

<211> 1366
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K24;R11 variant4)

<400> 19

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
165 170 175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
180 185 190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
195 200 205

Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
210 215 220

Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
Page 50

JPOXMLDOC01-seq1

225 230 235 240
 Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
 245 250 255
 Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
 260 265 270
 Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
 275 280 285
 Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro
 290 295 300
 Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
 305 310 315 320
 Arg Ala Lys Thr Ile Lys Asn Thr Val Cys Val Asn Val Glu Leu Thr
 325 330 335
 Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
 340 345 350
 Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
 355 360 365
 Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
 370 375 380
 Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
 385 390 395 400
 Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
 405 410 415
 Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 420 425 430
 Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 435 440 445
 Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
 450 455 460
 Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
 465 470 475 480
 Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
 485 490 495
 Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
 500 505 510

JPOXMLDOC01-seq1

500

505

510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
 515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
 530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
 545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
 565 570 575

Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
 580 585 590

Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
 595 600 605

Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
 610 615 620

Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln His Glu
 625 630 635 640

Ala Lys Ile Lys Ser Leu Thr Glu Tyr Leu Gln Asn Val Glu Gln Lys
 645 650 655

Lys Arg Gln Leu Glu Glu Ser Val Asp Ala Leu Ser Glu Glu Leu Val
 660 665 670

Gln Leu Arg Ala Gln Glu Lys Val His Glu Met Glu Lys Glu His Leu
 675 680 685

Asn Lys Val Gln Thr Ala Asn Glu Val Lys Gln Ala Val Glu Gln Gln
 690 695 700

Ile Gln Ser His Arg Glu Thr His Gln Lys Gln Ile Ser Ser Leu Arg
 705 710 715 720

Asp Glu Val Glu Ala Lys Ala Lys Leu Ile Thr Asp Leu Gln Asp Gln
 725 730 735

Asn Gln Lys Met Met Leu Glu Gln Glu Arg Leu Arg Val Glu His Glu
 740 745 750

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

Thr Val Met Gln Asp Arg Arg Glu Gln Ala Arg Gln Asp Leu Lys Gly
 Page 52

JPOXMLDOC01-seq1

770

775

780

Leu Glu Glu Thr Val Ala Lys Glu Leu Gln Thr Leu His Asn Leu Arg
 785 790 795 800

Lys Leu Phe Val Gln Asp Leu Ala Thr Arg Val Lys Lys Ser Ala Glu
 805 810 815

Ile Asp Ser Asp Asp Thr Gly Gly Ser Ala Ala Gln Lys Gln Lys Ile
 820 825 830

Ser Phe Leu Glu Asn Asn Leu Glu Gln Leu Thr Lys Val His Lys Gln
 835 840 845

Leu Val Arg Asp Asn Ala Asp Leu Arg Cys Glu Leu Pro Lys Leu Glu
 850 855 860

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

Leu Lys Glu Ala Lys Glu Asn Ala Ser Arg Asp Arg Lys Arg Tyr Gln
 885 890 895

Gln Glu Val Asp Arg Ile Lys Glu Ala Val Arg Ser Lys Asn Met Ala
 900 905 910

Arg Arg Gly His Ser Ala Gln Ile Asp Pro Leu Cys Asp Glu Leu Cys
 915 920 925

Arg Thr Val Ile Ala Ala Ala Val Leu Phe Ser Phe Ile Val Ser Val
 930 935 940

Leu Leu Ser Ala Phe Cys Ile His Cys Tyr His Lys Phe Ala His Lys
 945 950 955 960

Pro Pro Ile Ser Ser Ala Glu Met Thr Phe Arg Arg Pro Ala Gln Ala
 965 970 975

Phe Pro Val Ser Tyr Ser Ser Ser Gly Ala Arg Arg Pro Ser Leu Asp
 980 985 990

Ser Met Glu Asn Gln Val Ser Val Asp Ala Phe Lys Ile Leu Glu Asp
 995 1000 1005

Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr
 1010 1015 1020

Leu Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe
 1025 1030 1035

His Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met

JPOXMLDOC01-seq1

1040						1045						1050
Leu	Lys	Glu	Asn	Ala	Ser	Pro	Ser	Glu	Leu	Arg	Asp	Leu
	1055					1060					1065	Ser
Glu	Phe	Asn	Val	Leu	Lys	Gln	Val	Asn	His	Pro	His	Val
	1070					1075					1080	Ile
												Lys
Leu	Tyr	Gly	Ala	Cys	Ser	Gln	Asp	Gly	Pro	Leu	Leu	Leu
	1085					1090					1095	Ile
												Val
Glu	Tyr	Ala	Lys	Tyr	Gly	Ser	Leu	Arg	Gly	Phe	Leu	Arg
	1100					1105					1110	Glu
												Ser
Arg	Lys	Val	Gly	Pro	Gly	Tyr	Leu	Gly	Ser	Gly	Gly	Ser
	1115					1120					1125	Arg
												Asn
Ser	Ser	Ser	Leu	Asp	His	Pro	Asp	Glu	Arg	Ala	Leu	Thr
	1130					1135					1140	Met
												Gly
Asp	Leu	Ile	Ser	Phe	Ala	Trp	Gln	Ile	Ser	Gln	Gly	Met
	1145					1150					1155	Gln
												Tyr
Leu	Ala	Glu	Met	Lys	Leu	Val	His	Arg	Asp	Leu	Ala	Ala
	1160					1165					1170	Arg
												Asn
Ile	Leu	Val	Ala	Glu	Gly	Arg	Lys	Met	Lys	Ile	Ser	Asp
	1175					1180					1185	Phe
												Gly
Leu	Ser	Arg	Asp	Val	Tyr	Glu	Glu	Asp	Ser	Tyr	Val	Lys
	1190					1195					1200	Arg
												Ser
Gln	Gly	Arg	Ile	Pro	Val	Lys	Trp	Met	Ala	Ile	Glu	Ser
	1205					1210					1215	Leu
												Phe
Asp	His	Ile	Tyr	Thr	Thr	Gln	Ser	Asp	Val	Trp	Ser	Phe
	1220					1225					1230	Gly
												Val
Leu	Leu	Trp	Glu	Ile	Val	Thr	Leu	Gly	Gly	Asn	Pro	Tyr
	1235					1240					1245	Pro
												Gly
Ile	Pro	Pro	Glu	Arg	Leu	Phe	Asn	Leu	Leu	Lys	Thr	Gly
	1250					1255					1260	His
												Arg
Met	Glu	Arg	Pro	Asp	Asn	Cys	Ser	Glu	Glu	Met	Tyr	Arg
	1265					1270					1275	Leu
												Met
Leu	Gln	Cys	Trp	Lys	Gln	Glu	Pro	Asp	Lys	Arg	Pro	Val
	1280					1285					1290	Phe
												Ala
Asp	Ile	Ser	Lys	Asp	Leu	Glu	Lys	Met	Met	Val	Lys	Arg
												Arg
												Asp

JPOXMLDOC01-seq1

1295

1300

1305

Tyr Leu Asp Leu Ala Ala Ser Thr Pro Ser Asp Ser Leu Ile Tyr
1310 1315 1320

Asp Asp Gly Leu Ser Glu Glu Glu Thr Pro Leu Val Asp Cys Asn
1325 1330 1335

Asn Ala Pro Leu Pro Arg Ala Leu Pro Ser Thr Trp Ile Glu Asn
1340 1345 1350

Lys Leu Tyr Gly Arg Ile Ser His Ala Phe Thr Arg Phe
1355 1360 1365

<210> 20
<211> 977
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K15;R12 variant2)

<400> 20

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn

JPOXMLDOC01-seq1

145 150 155 160
 Arg Val Pro Tyr Val₁₆₅ Lys Gly Cys Thr Glu₁₇₀ Arg Phe Val Cys Ser₁₇₅ Pro
 Asp Glu Val Met₁₈₀ Asp Thr Ile Asp Glu₁₈₅ Gly Lys Ser Asn Arg₁₉₀ His Val
 Ala Val Thr₁₉₅ Asn Met Asn Glu His₂₀₀ Ser Ser Arg Ser His₂₀₅ Ser Ile Phe
 Leu Ile₂₁₀ Asn Val Lys Gln Glu₂₁₅ Asn Thr Gln Thr Glu₂₂₀ Gln Lys Leu Ser
 Gly₂₂₅ Lys Leu Tyr Leu Val₂₃₀ Asp Leu Ala Gly Ser₂₃₅ Glu Lys Val Ser Lys₂₄₀
 Thr Gly Ala Glu Gly₂₄₅ Ala Val Leu Asp Glu₂₅₀ Ala Lys Asn Ile Asn₂₅₅ Lys
 Ser Leu Ser Ala₂₆₀ Leu Gly Asn Val Ile₂₆₅ Ser Ala Leu Ala Glu₂₇₀ Gly Ser
 Thr Tyr Val₂₇₅ Pro Tyr Arg Asp Ser₂₈₀ Lys Met Thr Arg Ile₂₈₅ Leu Gln Asp
 Ser Leu₂₉₀ Gly Gly Asn Cys Arg₂₉₅ Thr Thr Ile Val Ile₃₀₀ Cys Cys Ser Pro
 Ser₃₀₅ Ser Tyr Asn Glu Ser₃₁₀ Glu Thr Lys Ser Thr₃₁₅ Leu Leu Phe Gly Gln₃₂₀
 Arg Ala Lys Thr Ile₃₂₅ Lys Asn Thr Val Cys₃₃₀ Val Asn Val Glu Leu₃₃₅ Thr
 Ala Glu Gln Trp₃₄₀ Lys Lys Lys Tyr Glu₃₄₅ Lys Glu Lys Glu Lys₃₅₀ Asn Lys
 Ile Leu Arg₃₅₅ Asn Thr Ile Gln Trp₃₆₀ Leu Glu Asn Glu Leu₃₆₅ Asn Arg Trp
 Arg Asn₃₇₀ Gly Glu Thr Val Pro₃₇₅ Ile Asp Glu Gln Phe₃₈₀ Asp Lys Glu Lys
 Ala₃₈₅ Asn Leu Glu Ala Phe₃₉₀ Thr Val Asp Lys Asp₃₉₅ Ile Thr Leu Thr Asn₄₀₀
 Asp Lys Pro Ala Thr₄₀₅ Ala Ile Gly Val Ile₄₁₀ Gly Asn Phe Thr Asp₄₁₅ Ala
 Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 Page 56

JPOXMLDOC01-seq1

420

425

430

Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 435 440 445

Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
 450 455 460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
 465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
 485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
 500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
 515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
 530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
 545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Glu
 565 570 575

Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr
 580 585 590

Leu Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe His
 595 600 605

Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys
 610 615 620

Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn
 625 630 635 640

Val Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala
 645 650 655

Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr
 660 665 670

Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly
 675 680 685

Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro
 Page 57

JPOXMLDOC01-seq1

690

695

700

Asp Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln
 705 710 715 720

Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg
 725 730 735

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

Ile Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr
 755 760 765

Val Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu
 770 775 780

Ser Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe
 785 790 795 800

Gly Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr Pro
 805 810 815

Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly His Arg
 820 825 830

Met Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu Met Leu
 835 840 845

Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala Asp Ile
 850 855 860

Ser Lys Asp Leu Glu Lys Met Met Val Lys Arg Arg Asp Tyr Leu Asp
 865 870 875 880

Leu Ala Ala Ser Thr Pro Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu
 885 890 895

Ser Glu Glu Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro
 900 905 910

Arg Ala Leu Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Met Ser
 915 920 925

Asp Pro Asn Trp Pro Gly Glu Ser Pro Val Pro Leu Thr Arg Ala Asp
 930 935 940

Gly Thr Asn Thr Gly Phe Pro Arg Tyr Pro Asn Asp Ser Val Tyr Ala
 945 950 955 960

Asn Trp Met Leu Ser Pro Ser Ala Ala Lys Leu Met Asp Thr Phe Asp

Ser

<210> 21
 <211> 1040
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> KIF5B-RET (K16;R12 variant2)

<400> 21

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
 1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
 20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
 35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
 50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
 65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
 85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
 100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
 115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
 145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
 165 170 175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
 180 185 190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
 Page 59

JPOXMLDOC01-seq1

195

200

205

Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
 210 215 220
 Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
 225 230 235 240
 Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
 245 250 255
 Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
 260 265 270
 Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
 275 280 285
 Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro
 290 295 300
 Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
 305 310 315 320
 Arg Ala Lys Thr Ile Lys Asn Thr Val Cys Val Asn Val Glu Leu Thr
 325 330 335
 Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
 340 345 350
 Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
 355 360 365
 Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
 370 375 380
 Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
 385 390 395 400
 Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
 405 410 415
 Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 420 425 430
 Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 435 440 445
 Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
 450 455 460
 Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu

JPOXMLDOC01-seq1

465 470 475 480
 Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
 485 490 495
 Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
 500 505 510
 Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
 515 520 525
 Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
 530 535 540
 Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
 545 550 555 560
 Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
 565 570 575
 Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
 580 585 590
 Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
 595 600 605
 Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
 610 615 620
 Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln Glu Asp
 625 630 635 640
 Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr Leu
 645 650 655
 Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe His Leu
 660 665 670
 Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys Glu
 675 680 685
 Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn Val
 690 695 700
 Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala Cys
 705 710 715 720
 Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly
 725 730 735
 Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr
 740 745 750
 Page 61

JPOXMLDOC01-seq1

740

745

750

Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro Asp
755 760 765

Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile
770 775 780

Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg Asp
785 790 795 800

Leu Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys Met Lys Ile
805 810 815

Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val
820 825 830

Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu Ser
835 840 845

Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe Gly
850 855 860

Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr Pro Gly
865 870 875 880

Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly His Arg Met
885 890 895

Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu Met Leu Gln
900 905 910

Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala Asp Ile Ser
915 920 925

Lys Asp Leu Glu Lys Met Met Val Lys Arg Arg Asp Tyr Leu Asp Leu
930 935 940

Ala Ala Ser Thr Pro Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu Ser
945 950 955 960

Glu Glu Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg
965 970 975

Ala Leu Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Met Ser Asp
980 985 990

Pro Asn Trp Pro Gly Glu Ser Pro Val Pro Leu Thr Arg Ala Asp Gly
995 1000 1005

Thr Asn Thr Gly Phe Pro Arg Tyr Pro Asn Asp Ser Val Tyr Ala

JPOXMLDOC01-seq1

1010

1015

1020

Asn Trp Met Leu Ser Pro Ser Ala Ala Lys Leu Met Asp Thr Phe
1025 1030 1035

Asp Ser
1040

<210> 22
<211> 1215
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K22;R12 variant2)

<400> 22

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
165 170 175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
Page 63

JPOXMLDOC01-seq1

180

185

190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
 195 200 205
 Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
 210 215 220
 Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
 225 230 235 240
 Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
 245 250 255
 Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
 260 265 270
 Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
 275 280 285
 Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro
 290 295 300
 Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
 305 310 315 320
 Arg Ala Lys Thr Ile Lys Asn Thr Val Cys Val Asn Val Glu Leu Thr
 325 330 335
 Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
 340 345 350
 Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
 355 360 365
 Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
 370 375 380
 Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
 385 390 395 400
 Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
 405 410 415
 Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 420 425 430
 Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 435 440 445
 Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg

JPOXMLDOC01-seq1

450

455

460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
565 570 575

Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
580 585 590

Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
595 600 605

Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
610 615 620

Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln His Glu
625 630 635 640

Ala Lys Ile Lys Ser Leu Thr Glu Tyr Leu Gln Asn Val Glu Gln Lys
645 650 655

Lys Arg Gln Leu Glu Glu Ser Val Asp Ala Leu Ser Glu Glu Leu Val
660 665 670

Gln Leu Arg Ala Gln Glu Lys Val His Glu Met Glu Lys Glu His Leu
675 680 685

Asn Lys Val Gln Thr Ala Asn Glu Val Lys Gln Ala Val Glu Gln Gln
690 695 700

Ile Gln Ser His Arg Glu Thr His Gln Lys Gln Ile Ser Ser Leu Arg
705 710 715 720

Asp Glu Val Glu Ala Lys Ala Lys Leu Ile Thr Asp Leu Gln Asp Gln

JPOXMLDOC01-seq1

725

730

735

Asn Gln Lys Met Met Leu Glu Gln Glu Arg Leu Arg Val Glu His Glu
740 745 750

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

Thr Val Met Gln Asp Arg Arg Glu Gln Ala Arg Gln Asp Leu Lys Gly
770 775 780

Leu Glu Glu Thr Val Ala Lys Glu Leu Gln Thr Leu His Asn Leu Arg
785 790 795 800

Lys Leu Phe Val Gln Asp Leu Ala Thr Arg Val Lys Lys Glu Asp Pro
805 810 815

Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr Leu Gly
820 825 830

Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe His Leu Lys
835 840 845

Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys Glu Asn
850 855 860

Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn Val Leu
865 870 875 880

Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala Cys Ser
885 890 895

Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly Ser
900 905 910

Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr Leu
915 920 925

Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro Asp Glu
930 935 940

Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile Ser
945 950 955 960

Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg Asp Leu
965 970 975

Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys Met Lys Ile Ser
980 985 990

Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val Lys

Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu Ser
1010 1015 1020

Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe
1025 1030 1035

Gly Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr
1040 1045 1050

Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly
1055 1060 1065

His Arg Met Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg
1070 1075 1080

Leu Met Leu Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val
1085 1090 1095

Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys Met Met Val Lys Arg
1100 1105 1110

Arg Asp Tyr Leu Asp Leu Ala Ala Ser Thr Pro Ser Asp Ser Leu
1115 1120 1125

Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu Thr Pro Leu Val Asp
1130 1135 1140

Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu Pro Ser Thr Trp Ile
1145 1150 1155

Glu Asn Lys Leu Tyr Gly Met Ser Asp Pro Asn Trp Pro Gly Glu
1160 1165 1170

Ser Pro Val Pro Leu Thr Arg Ala Asp Gly Thr Asn Thr Gly Phe
1175 1180 1185

Pro Arg Tyr Pro Asn Asp Ser Val Tyr Ala Asn Trp Met Leu Ser
1190 1195 1200

Pro Ser Ala Ala Lys Leu Met Asp Thr Phe Asp Ser
1205 1210 1215

<210> 23
<211> 1250
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K23;R12 variant2)

JPOXMLDOC01-seq1

<400> 23

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
165 170 175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
180 185 190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
195 200 205

Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
210 215 220

Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
225 230 235 240

Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
245 250 255

Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
Page 68

JPOXMLDOC01-seq1

260

265

270

Thr Tyr Val₂₇₅ Pro Tyr Arg Asp Ser₂₈₀ Lys Met Thr Arg Ile₂₈₅ Leu Gln Asp
 Ser Leu₂₉₀ Gly Gly Asn Cys Arg₂₉₅ Thr Thr Ile Val Ile₃₀₀ Cys Cys Ser Pro
 Ser₃₀₅ Ser Tyr Asn Glu Ser₃₁₀ Glu Thr Lys Ser Thr₃₁₅ Leu Leu Phe Gly Gln₃₂₀
 Arg Ala Lys Thr Ile₃₂₅ Lys Asn Thr Val Cys₃₃₀ Val Asn Val Glu Leu₃₃₅ Thr
 Ala Glu Gln Trp₃₄₀ Lys Lys Lys Tyr Glu₃₄₅ Lys Glu Lys Glu Lys₃₅₀ Asn Lys
 Ile Leu Arg₃₅₅ Asn Thr Ile Gln Trp₃₆₀ Leu Glu Asn Glu Leu₃₆₅ Asn Arg Trp
 Arg Asn₃₇₀ Gly Glu Thr Val Pro₃₇₅ Ile Asp Glu Gln Phe₃₈₀ Asp Lys Glu Lys
 Ala₃₈₅ Asn Leu Glu Ala Phe₃₉₀ Thr Val Asp Lys Asp₃₉₅ Ile Thr Leu Thr Asn₄₀₀
 Asp Lys Pro Ala Thr₄₀₅ Ala Ile Gly Val Ile₄₁₀ Gly Asn Phe Thr Asp₄₁₅ Ala
 Glu Arg Arg Lys₄₂₀ Cys Glu Glu Glu Ile₄₂₅ Ala Lys Leu Tyr Lys₄₃₀ Gln Leu
 Asp Asp Lys₄₃₅ Asp Glu Glu Ile Asn₄₄₀ Gln Gln Ser Gln Leu₄₄₅ Val Glu Lys
 Leu Lys₄₅₀ Thr Gln Met Leu Asp₄₅₅ Gln Glu Glu Leu Leu₄₆₀ Ala Ser Thr Arg
 Arg₄₆₅ Asp Gln Asp Asn Met₄₇₀ Gln Ala Glu Leu Asn₄₇₅ Arg Leu Gln Ala Glu₄₈₀
 Asn Asp Ala Ser Lys₄₈₅ Glu Glu Val Lys Glu₄₉₀ Val Leu Gln Ala Leu₄₉₅ Glu
 Glu Leu Ala Val₅₀₀ Asn Tyr Asp Gln Lys₅₀₅ Ser Gln Glu Val Glu₅₁₀ Asp Lys
 Thr Lys Glu₅₁₅ Tyr Glu Leu Leu Ser₅₂₀ Asp Glu Leu Asn Gln₅₂₅ Lys Ser Ala
 Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr

JPOXMLDOC01-seq1

530

535

540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
565 570 575

Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
580 585 590

Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
595 600 605

Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
610 615 620

Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln His Glu
625 630 635 640

Ala Lys Ile Lys Ser Leu Thr Glu Tyr Leu Gln Asn Val Glu Gln Lys
645 650 655

Lys Arg Gln Leu Glu Glu Ser Val Asp Ala Leu Ser Glu Glu Leu Val
660 665 670

Gln Leu Arg Ala Gln Glu Lys Val His Glu Met Glu Lys Glu His Leu
675 680 685

Asn Lys Val Gln Thr Ala Asn Glu Val Lys Gln Ala Val Glu Gln Gln
690 695 700

Ile Gln Ser His Arg Glu Thr His Gln Lys Gln Ile Ser Ser Leu Arg
705 710 715 720

Asp Glu Val Glu Ala Lys Ala Lys Leu Ile Thr Asp Leu Gln Asp Gln
725 730 735

Asn Gln Lys Met Met Leu Glu Gln Glu Arg Leu Arg Val Glu His Glu
740 745 750

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

Thr Val Met Gln Asp Arg Arg Glu Gln Ala Arg Gln Asp Leu Lys Gly
770 775 780

Leu Glu Glu Thr Val Ala Lys Glu Leu Gln Thr Leu His Asn Leu Arg
785 790 795 800

Lys Leu Phe Val Gln Asp Leu Ala Thr Arg Val Lys Lys Ser Ala Glu

JPOXMLDOC01-seq1

805

810

815

Ile Asp Ser Asp Asp Thr Gly Gly Ser Ala Ala Gln Lys Gln Lys Ile
 820 825 830

Ser Phe Leu Glu Asn Asn Leu Glu Gln Leu Thr Lys Val His Lys Gln
 835 840 845

Glu Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys
 850 855 860

Thr Leu Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe
 865 870 875 880

His Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu
 885 890 895

Lys Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe
 900 905 910

Asn Val Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly
 915 920 925

Ala Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys
 930 935 940

Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro
 945 950 955 960

Gly Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His
 965 970 975

Pro Asp Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp
 980 985 990

Gln Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His
 995 1000 1005

Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys
 1010 1015 1020

Met Lys Ile Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu
 1025 1030 1035

Asp Ser Tyr Val Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp
 1040 1045 1050

Met Ala Ile Glu Ser Leu Phe Asp His Ile Tyr Thr Thr Gln Ser
 1055 1060 1065

Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Val Thr Leu
 Page 71

JPOXMLDOC01-seq1

1070

1075

1080

Gly Gly Asn Pro Tyr Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn
1085 1090 1095

Leu Leu Lys Thr Gly His Arg Met Glu Arg Pro Asp Asn Cys Ser
1100 1105 1110

Glu Glu Met Tyr Arg Leu Met Leu Gln Cys Trp Lys Gln Glu Pro
1115 1120 1125

Asp Lys Arg Pro Val Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys
1130 1135 1140

Met Met Val Lys Arg Arg Asp Tyr Leu Asp Leu Ala Ala Ser Thr
1145 1150 1155

Pro Ser Asp Ser Leu Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu
1160 1165 1170

Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu
1175 1180 1185

Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Met Ser Asp Pro
1190 1195 1200

Asn Trp Pro Gly Glu Ser Pro Val Pro Leu Thr Arg Ala Asp Gly
1205 1210 1215

Thr Asn Thr Gly Phe Pro Arg Tyr Pro Asn Asp Ser Val Tyr Ala
1220 1225 1230

Asn Trp Met Leu Ser Pro Ser Ala Ala Lys Leu Met Asp Thr Phe
1235 1240 1245

Asp Ser
1250

<210> 24
<211> 985
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B-RET (K15;R11 variant4)

<400> 24

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
 35 40 45
 Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
 50 55 60
 Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
 65 70 75 80
 Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
 85 90 95
 Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
 100 105 110
 Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
 115 120 125
 His Ile Lys Val Ser Tyr Phe Glu Ile Tyr Leu Asp Lys Ile Arg Asp
 130 135 140
 Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
 145 150 155 160
 Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
 165 170 175
 Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
 180 185 190
 Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
 195 200 205
 Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
 210 215 220
 Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
 225 230 235 240
 Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
 245 250 255
 Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
 260 265 270
 Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
 275 280 285
 Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro

JPOXMLDOC01-seq1

290

295

300

Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
 305 310 315 320

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

Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
 340 345 350

Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
 355 360 365

Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
 370 375 380

Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
 385 390 395 400

Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
 405 410 415

Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
 420 425 430

Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
 435 440 445

Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
 450 455 460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
 465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
 485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
 500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
 515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
 530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
 545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Phe
 Page 74

Ala His Lys Pro Pro Ile Ser Ser Ala Glu Met Thr Phe Arg Arg Pro
580 585 590

Ala Gln Ala Phe Pro Val Ser Tyr Ser Ser Ser Gly Ala Arg Arg Pro
595 600 605

Ser Leu Asp Ser Met Glu Asn Gln Val Ser Val Asp Ala Phe Lys Ile
610 615 620

Leu Glu Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly
625 630 635 640

Lys Thr Leu Gly Glu Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala
645 650 655

Phe His Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met
660 665 670

Leu Lys Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu
675 680 685

Phe Asn Val Leu Lys Gln Val Asn His Pro His Val Ile Lys Leu Tyr
690 695 700

Gly Ala Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala
705 710 715 720

Lys Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly
725 730 735

Pro Gly Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp
740 745 750

His Pro Asp Glu Arg Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala
755 760 765

Trp Gln Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val
770 775 780

His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys
785 790 795 800

Met Lys Ile Ser Asp Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp
805 810 815

Ser Tyr Val Lys Arg Ser Gln Gly Arg Ile Pro Val Lys Trp Met Ala
820 825 830

Ile Glu Ser Leu Phe Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp

835 JPOXMLDOC01-seq1 840 845

Ser Phe Gly Val Leu Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro
850 855 860

Tyr Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly
865 870 875 880

His Arg Met Glu Arg Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu
885 890 895

Met Leu Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala
900 905 910

Asp Ile Ser Lys Asp Leu Glu Lys Met Met Val Lys Arg Arg Asp Tyr
915 920 925

Leu Asp Leu Ala Ala Ser Thr Pro Ser Asp Ser Leu Ile Tyr Asp Asp
930 935 940

Gly Leu Ser Glu Glu Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro
945 950 955 960

Leu Pro Arg Ala Leu Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly
965 970 975

Arg Ile Ser His Ala Phe Thr Arg Phe
980 985

<210> 25
<211> 1512
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> CCDC6-RET variant a (AB698668.1)

<400> 25
atggcggaca gcgccagcga gagcgacacg gacggggcgg ggggcaacag cagcagctcg 60
gccgccatgc agtcgtcctg ctcgtcgacc tcgggcgggcgc gcggtggcgg cgggggagggc 120
ggcggcggtg ggaagtcggg gggcattgtc atctcgccgt tccgcctgga ggagctcacc 180
aaccgcctgg ctcgctgca gcaagagaac aaggtgctga agatagagct ggagacctac 240
aaactgaagt gcaaggcact gcaggaggag aaccgcgacc tgcgcaaagc cagcgttacc 300
atcgaggatc caaagtggga attccctcgg aagaacttgg ttcttgga aaactctagga 360
gaaggcgaat ttggaaaagt ggtcaaggca acggccttcc atctgaaagg cagagcaggg 420
tacaccacgg tggccgtgaa gatgctgaaa gagaacgcct ccccgagtga gctgcgagac 480
ctgctgtcag agttcaacgt cctgaagcag gtcaaccacc cacatgtcat caaattgtat 540

JPOXMLDOC01-seq1

ggggcctgca gccaggatgg cccgctcctc ctcacgtgag agtacgcaa atacggctcc	600
ctgcggggct tcctccgcga gagccgcaaa gtggggcctg gctacctggg cagtggaggc	660
agccgcaact ccagctccct ggaccacccg gatgagcggg ccctcaccat gggcgacctc	720
atctcatttg cctggcagat ctcacagggg atgcagtatc tggccgagat gaagctcggt	780
catcgggact tggcagccag aaacatcctg gtagctgagg ggcggaagat gaagatttcg	840
gatttcggct tgtcccgaga tgtttatgaa gaggattcct acgtgaagag gagccagggt	900
cggattccag ttaaatggat ggcaattgaa tccctttttg atcatatcta caccacgcaa	960
agtgatgtat ggtctttttg tgtcctgctg tgggagatcg tgaccctagg gggaaacccc	1020
tatcctggga ttctctctga gcggctcttc aaccttctga agaccggcca ccggatggag	1080
aggccagaca actgcagcga ggagatgtac cgcctgatgc tgcaatgctg gaagcaggag	1140
ccggacaaaa ggccggtggt tgcggacatc agcaaagacc tggagaagat gatggttaag	1200
aggagagact acttgacct tgcggcgctc actccatctg actccctgat ttatgacgac	1260
ggcctctcag aggaggagac accgctgggtg gactgtaata atgccccct ccctcgagcc	1320
ctcccttcca catggattga aaacaaactc tatggcatgt cagacccgaa ctggcctgga	1380
gagagtcctg taccactcac gagagctgat ggcactaaca ctgggtttcc aagatatcca	1440
aatgatagtg tatatgctaa ctggatgctt tcaccctcag cggcaaaatt aatggacacg	1500
tttgatagtt aa	1512

<210> 26
 <211> 1386
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CCDC6-RET variant c (AB698669.1)

<400> 26	
atggcggaca gcgccagcga gagcgacacg gacggggcgg ggggcaacag cagcagctcg	60
gccgccatgc agtcgtcctg ctcgtcgacc tcgggcggcg gcggtggcgg cgggggaggc	120
ggcggcgggtg ggaagtcggg gggcattgtc atctcgccgt tccgcctgga ggagctcacc	180
aaccgcctgg cctcgctgca gcaagagaac aagggtgctga agatagagct ggagacctac	240
aaactgaagt gcaaggcact gcaggaggag aaccgcgacc tgcgcaaagc cagcgttacc	300
atcgaggatc caaagtggga attccctcgg aagaacttgg ttcttgga aaactctagga	360
gaaggcgaat ttggaaaagt ggtcaaggca acggccttcc atctgaaagg cagagcaggg	420
tacaccacgg tggccgtgaa gatgctgaaa gagaacgcct ccccgagtga gctgcgagac	480
ctgctgtcag agttcaacgt cctgaagcag gtcaaccacc cacatgtcat caaattgtat	540
ggggcctgca gccaggatgg cccgctcctc ctcacgtgag agtacgcaa atacggctcc	600
ctgcggggct tcctccgcga gagccgcaaa gtggggcctg gctacctggg cagtggaggc	660

JPOXMLDOC01-seq1

agccgcaact ccagctccct ggaccacccg gatgagcggg ccctcaccat gggcgacctc 720
atctcatttg cctggcagat ctcacagggg atgcagtatc tggccgagat gaagctcggt 780
catcgggact tggcagccag aaacatcctg gtagctgagg ggcggaagat gaagatttcg 840
gatttcggct tgtcccgaga tgtttatgaa gaggattcct acgtgaagag gagccagggt 900
cggattccag ttaaattggat ggcaattgaa tccctttttg atcatatcta caccacgcaa 960
agtgatgtat ggtcttttgg tgcctgctg tgggagatcg tgaccctagg gggaaacccc 1020
tattctggga ttctctctga gcggctcttc aaccttctga agaccggcca ccggatggag 1080
aggccagaca actgcagcga ggagatgtac cgcctgatgc tgcaatgctg gaagcaggag 1140
ccggacaaaa ggccggtggt tgcggacatc agcaaagacc tggagaagat gatggttaag 1200
aggagagact acttggacct tgcggcgctc actccatctg actccctgat ttatgacgac 1260
ggcctctcag aggaggagac accgctgggt gactgtaata atgccccct ccctcgagcc 1320
ctcccttcca catggattga aaacaaactc tatggtagaa tttcccatgc atttactaga 1380
ttctag 1386

<210> 27
<211> 503
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> CCDC6-RET variant a (BAM36435.1)

<400> 27

Met Ala Asp Ser Ala Ser Glu Ser Asp Thr Asp Gly Ala Gly Gly Asn
1 5 10 15

Ser Ser Ser Ser Ala Ala Met Gln Ser Ser Cys Ser Ser Thr Ser Gly
20 25 30

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Lys Ser Gly Gly
35 40 45

Ile Val Ile Ser Pro Phe Arg Leu Glu Glu Leu Thr Asn Arg Leu Ala
50 55 60

Ser Leu Gln Gln Glu Asn Lys Val Leu Lys Ile Glu Leu Glu Thr Tyr
65 70 75 80

Lys Leu Lys Cys Lys Ala Leu Gln Glu Glu Asn Arg Asp Leu Arg Lys
85 90 95

Ala Ser Val Thr Ile Glu Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn
100 105 110

Leu Val Leu Gly Lys Thr Leu Gly Glu Gly Glu Phe Gly Lys Val Val

JPOXMLDOC01-seq1

115

120

125

Lys Ala Thr Ala Phe His Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val
 130 135 140
 Ala Val Lys Met Leu Lys Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp
 145 150 155 160
 Leu Leu Ser Glu Phe Asn Val Leu Lys Gln Val Asn His Pro His Val
 165 170 175
 Ile Lys Leu Tyr Gly Ala Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile
 180 185 190
 Val Glu Tyr Ala Lys Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser
 195 200 205
 Arg Lys Val Gly Pro Gly Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser
 210 215 220
 Ser Ser Leu Asp His Pro Asp Glu Arg Ala Leu Thr Met Gly Asp Leu
 225 230 235 240
 Ile Ser Phe Ala Trp Gln Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu
 245 250 255
 Met Lys Leu Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ala
 260 265 270
 Glu Gly Arg Lys Met Lys Ile Ser Asp Phe Gly Leu Ser Arg Asp Val
 275 280 285
 Tyr Glu Glu Asp Ser Tyr Val Lys Arg Ser Gln Gly Arg Ile Pro Val
 290 295 300
 Lys Trp Met Ala Ile Glu Ser Leu Phe Asp His Ile Tyr Thr Thr Gln
 305 310 315 320
 Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Val Thr Leu
 325 330 335
 Gly Gly Asn Pro Tyr Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu
 340 345 350
 Leu Lys Thr Gly His Arg Met Glu Arg Pro Asp Asn Cys Ser Glu Glu
 355 360 365
 Met Tyr Arg Leu Met Leu Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg
 370 375 380
 Pro Val Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys Met Met Val Lys

JPOXMLDOC01-seq1

Ala Ser Val Thr Ile Glu Asp Pro Lys Trp Glu Phe Pro Arg Lys Asn
Page 80

JPOXMLDOC01-seq1

100

105

110

Leu Val Leu Gly Lys Thr Leu Gly Glu Gly Glu Phe Gly Lys Val Val
 115 120 125
 Lys Ala Thr Ala Phe His Leu Lys Gly Arg Ala Gly Tyr Thr Thr Val
 130 135 140
 Ala Val Lys Met Leu Lys Glu Asn Ala Ser Pro Ser Glu Leu Arg Asp
 145 150 155 160
 Leu Leu Ser Glu Phe Asn Val Leu Lys Gln Val Asn His Pro His Val
 165 170 175
 Ile Lys Leu Tyr Gly Ala Cys Ser Gln Asp Gly Pro Leu Leu Leu Ile
 180 185 190
 Val Glu Tyr Ala Lys Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser
 195 200 205
 Arg Lys Val Gly Pro Gly Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser
 210 215 220
 Ser Ser Leu Asp His Pro Asp Glu Arg Ala Leu Thr Met Gly Asp Leu
 225 230 235 240
 Ile Ser Phe Ala Trp Gln Ile Ser Gln Gly Met Gln Tyr Leu Ala Glu
 245 250 255
 Met Lys Leu Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Ala
 260 265 270
 Glu Gly Arg Lys Met Lys Ile Ser Asp Phe Gly Leu Ser Arg Asp Val
 275 280 285
 Tyr Glu Glu Asp Ser Tyr Val Lys Arg Ser Gln Gly Arg Ile Pro Val
 290 295 300
 Lys Trp Met Ala Ile Glu Ser Leu Phe Asp His Ile Tyr Thr Thr Gln
 305 310 315 320
 Ser Asp Val Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Val Thr Leu
 325 330 335
 Gly Gly Asn Pro Tyr Pro Gly Ile Pro Pro Glu Arg Leu Phe Asn Leu
 340 345 350
 Leu Lys Thr Gly His Arg Met Glu Arg Pro Asp Asn Cys Ser Glu Glu
 355 360 365
 Met Tyr Arg Leu Met Leu Gln Cys Trp Lys Gln Glu Pro Asp Lys Arg

JPOXMLDOC01-seq1

370

375

380

Pro Val Phe Ala Asp Ile Ser Lys Asp Leu Glu Lys Met Met Val Lys
385 390 395 400

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

Ile Tyr Asp Asp Gly Leu Ser Glu Glu Glu Thr Pro Leu Val Asp Cys
420 425 430

Asn Asn Ala Pro Leu Pro Arg Ala Leu Pro Ser Thr Trp Ile Glu Asn
435 440 445

Lys Leu Tyr Gly Arg Ile Ser His Ala Phe Thr Arg Phe
450 455 460

<210> 29
<211> 5905
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> KIF5B (NM_004521.2)

<400> 29
ctcctcccgc accgccctgt cgcccaacgg cggcctcagg agtgatcggg cagcagtcgg 60
ccggccagcg gacggcagag cgggcggacg ggtaggcccc gcctgctctt cgcgaggagg 120
aagaaggtgg ccactctccc ggtccccaga acctccccag ccccgagcgt ccgcccagac 180
cgtaaagggg gacgctgagg agccgcggac gctctccccg gtgccgccgc cgctgccgcc 240
gcatggctg ccatgatgga tcggaagtga gcattagggt taacggctgc cggcgccggc 300
tcttcaagtc ccggctcccc ggccgcctcc acccggggaa gcgcagcgcg gcgcagctga 360
ctgctgcctc tcacggccct cgcgaccaca agccctcagg tccggcgctt tccctgcaag 420
actgagcggc ggggagtggc tcccggccgc cggccccggc tgcgagaaag atggcggacc 480
tgcccgagtg caacatcaaa gtgatgtgtc gcttcagacc tctcaacgag tctgaagtga 540
accgcggcga caagtacatc gccaaagtttc agggagaaga cacggctcgtg atcgcgcca 600
agccttatgc atttgatcgg gtgttccagt caagcacatc tcaagagcaa gtgtataatg 660
actgtgcaaa gaagattggt aaagatgtac ttgaaggata taatggaaca atatttgc 720
atggacaaac atcctctggg aagacacaca caatggaggg taaacttcat gatccagaag 780
gcatgggaat tattccaaga atagtgaag atatttttaa ttatatttac tccatggatg 840
aaaatttgga atttcatatt aaggtttcat attttgaaat atatttggat aagataaggg 900
acctgttaga tgtttcaaag accaaccttt cagttcatga agacaaaaac cgagttccct 960
atgtaaaggg gtgcacagag cgttttgtat gtagtccaga tgaagttatg gataccatag 1020

JPOXMLDOC01-seq1

atgaaggaaa	atccaacaga	catgtagcag	ttacaaatat	gaatgaacat	agctctagga	1080
gtcacagtat	atttcttatt	aatgtcaaac	aagagaacac	acaaacggaa	caaaagctga	1140
gtggaaaact	ttatctgggt	gatttagctg	gtagtgaaaa	ggttagtaaa	actggagctg	1200
aaggtgctgt	gctggatgaa	gctaaaaaca	tcaacaagtc	actttctgct	cttggaatg	1260
ttattttctgc	tttggctgag	ggtagtacat	atgttccata	tcgagatagt	aaaatgacaa	1320
gaatccttca	agattcatta	ggtggcaact	gtagaaccac	tattgtaatt	tgctgctctc	1380
catcatcata	caatgagtct	gaaacaaaat	ctacactctt	atttggccaa	agggccaaaa	1440
caattaagaa	cacagtttgt	gtcaatgtgg	agttaactgc	agaacagtgg	aaaaagaagt	1500
atgaaaaaga	aaaagaaaaa	aataagatcc	tgcggaacac	tattcagtgg	cttgaaaatg	1560
agctcaacag	atggcgtaat	ggggagacgg	tgcctattga	tgaacagttt	gacaaagaga	1620
aagccaactt	ggaagctttc	acagtggata	aagatattac	tcttaccaat	gataaaccag	1680
caaccgcaat	tggagttata	ggaaatttta	ctgatgctga	aagaagaaag	tgtgaagaag	1740
aaattgctaa	attatacaaa	cagcttgatg	acaaggatga	agaaattaac	cagcaaagtc	1800
aactggtaga	gaaactgaag	acgcaaagt	tggatcagga	ggagcttttg	gcatctacca	1860
gaagggatca	agacaatatg	caagctgagc	tgaatcgctt	tcaagcagaa	aatgatgcct	1920
ctaaagaaga	agtgaagaa	gttttacagg	ccctagaaga	acttgctgtc	aattatgatc	1980
agaagtctca	ggaagttgaa	gacaaaacta	aggaatatga	attgcttagt	gatgaattga	2040
atcagaaatc	ggcaacttta	gcgagtatag	atgctgagct	tcagaaactt	aaggaaatga	2100
ccaaccacca	gaaaaaacga	gcagctgaga	tgatggcatc	tttactaaaa	gaccttgacg	2160
aataggaat	tgctgtggga	aataatgatg	taaagcagcc	tgaggggaact	ggcatgatag	2220
atgaagagtt	cactgttgca	agactctaca	ttagcaaaat	gaagtcagaa	gtaaaaacca	2280
tggtgaaacg	ttgcaagcag	ttagaaagca	cacaaactga	gagcaacaaa	aaaatggaag	2340
aaaatgaaaa	ggagttagca	gcatgtcagc	ttcgtatctc	tcaacatgaa	gccaaaatca	2400
agtcattgac	tgaatacctt	caaaatgtgg	aacaaaagaa	aagacagttg	gaggaatctg	2460
tcgatgccct	cagtgaagaa	ctagtccagc	ttcgagcaca	agagaaagtc	catgaaatgg	2520
aaaaggagca	cttaaataag	gttcagactg	caaatgaagt	taagcaagct	gttgaacagc	2580
agatccagag	ccatagagaa	actcatcaaa	aacagatcag	tagtttgaga	gatgaagtag	2640
aagcaaaagc	aaaacttatt	actgatcttc	aagacaaaaa	ccagaaaatg	atgttagagc	2700
aggaacgtct	aagagtagaa	catgagaagt	tgaaagccac	agatcaggaa	aagagcagaa	2760
aactacatga	acttacgggt	atgcaagata	gacgagaaca	agcaagacaa	gacttgaagg	2820
gtttggaaga	gacagtggca	aaagaacttc	agactttaca	caacctgcgc	aaactctttg	2880
ttcaggacct	ggctacaaga	gttaaaaaga	gtgctgagat	tgattctgat	gacaccggag	2940
gcagcgctgc	tcagaagcaa	aaaatctcct	ttcttgaaaa	taatcttgaa	cagctcacta	3000
aagtgcacaa	acagttggta	cgtgataatg	cagatctccg	ctgtgaactt	cctaagttgg	3060

JPOXMLDOC01-seq1

aaaagcgact	tcgagctaca	gctgagagag	tgaaagcttt	ggaatcagca	ctgaaagaag	3120
ctaaagaaaa	tgcattctcg	gatcgcaaac	gctatcagca	agaagtagat	cgcataaagg	3180
aagcagtcag	gtcaaagaat	atggccagaa	gagggcattc	tgcacagatt	gctaaaccta	3240
ttcgtcccgg	gcaacatcca	gcagcttctc	caactcacc	aagtgcatt	cgtggaggag	3300
gtgcatttgt	tcagaacagc	cagccagtgg	cagtgcgagg	tggaggaggc	aaacaagtgt	3360
aatcgtttat	acataccac	aggtgttaaa	aagtaatcga	agtacgaaga	ggacatggta	3420
tcaagcagtc	attcaatgac	tataacctct	actcccttgg	gattgtagaa	ttataacttt	3480
taaaaaaaaat	gtataaatta	tacctggcct	gtacagctgt	ttcctaccta	ctcttcttgt	3540
aaactctgct	gcttcccaac	acaactagag	tgcaattttg	gcatcttagg	agggaaaaag	3600
gacagtttac	aactgtggcc	ctatttatta	cacagtttgt	ctatcgtgtc	ttaaatttag	3660
tctttactgt	gccaaagctaa	ctgtacctta	taggactgta	ctttttgtat	tttttgtgta	3720
tgtttatttt	ttaatctcag	tttaaattac	ctagctgcta	ctgcttcttg	tttttctttt	3780
cctattaaaa	cgtcttcctt	tttttttctt	aagagaaaat	ggaacattta	ggttaaattgt	3840
ctttaaattt	taccacttaa	caacactaca	tgcccataaa	atatatccag	tcagtactgt	3900
attttaaaat	cccttgaaat	gatgatata	gggttaaaat	tacttgtatt	gtttctgaag	3960
tttgctcctg	aaaactactg	tttgagcact	gaaacgttac	aaatgcctaa	taggcatttg	4020
agactgagca	aggctacttg	ttatctcatg	aatgcctgt	tgccgagtta	ttttgaatag	4080
aaatatttta	aagtatcaaa	agcagatctt	agttaaaggg	agtttggaag	aggaattata	4140
tttctctttt	tcctgattct	gtactcaaca	agtcttgatg	gaattaaaat	actctgcttt	4200
attctgggtga	gcctgctagc	taatataagt	attggacagg	taataatttg	tcattcttta	4260
tattagtaaa	atgaattaag	atattatagg	attaaacata	attttatacg	gttagtactt	4320
tattggccga	cctaaattta	tagcgtgtgg	aaattgagaa	aatgaagaa	acaggacaga	4380
tatatgatga	attaaaaata	tatataggtc	aattttggtc	tgaaatccct	gaggtgtttt	4440
taacctgcta	cactaatttg	tacactaatt	tatttcttta	gtctagaaat	agtaaattgt	4500
ttgcaagtca	ctaataatca	ttagataaat	tatttcttgg	gccatagccg	ataattttgt	4560
aatcagtact	aagtgtatac	gtatttttgc	cactttttcc	tcagatgatt	aaagtaagtc	4620
aacagcttat	tttaggaaac	tgtaaaagta	atagggaaag	agatttcact	atttgcttca	4680
tcagtggtag	gggggcggtg	actgcaactg	tgtagcaga	aattcacaga	gaatggggat	4740
ttaagggttag	cagagaaact	tggaaagttc	tgtgttagga	tcttgctggc	agaattaact	4800
ttttgcaaaa	gttttataca	cagatatattg	tattaaattt	ggagccatag	tcagaagact	4860
cagatcataa	ttggcttatt	tttctatttc	cgtaactatt	gtaatttcca	cttttgtaat	4920
aattttgatt	taaaatataa	atttatttat	ttattttttt	aatagtcaaa	aatctttgct	4980
gttgtagtct	gcaacctcta	aatgatttgt	gttgctttta	ggattgatca	gaagaaacac	5040
tccaaaaatt	gagatgaaat	gttggtgcag	ccagttataa	gtaatatagt	taacaagcaa	5100

JPOXMLDOC01-seq1

aaaaagtgct gccacctttt atgatgattt tctaaatgga gaaacatttg gctgcatcca 5160
 catagacctt tatgttttgt tttcagttga aaacttgcct cctttggcaa cattcgtaaa 5220
 tgaagcagaa ttttttttcc tcttttttcc aaatatgtta gttttgttct tgtaagatgt 5280
 atcatgggta ttggtgctgt gtaatgaaca acgaatttta attagcatgt ggttcagaat 5340
 atacaatgtt aggtttttta aaagtatctt gatggttctt ttctatttat aatttcagac 5400
 tttcataaag tgtaccaaga atttcataaa tttgttttca gtgaactgct ttttgctatg 5460
 gtaggtcatt aaacacagca cttactctta aaaatgaaaa tttctgatca tctaggatat 5520
 tgacacattt caatttgcag tgtctttttg actggatata ttaacgttcc tctgaatggc 5580
 attgatagat ggttcagaag agaaactcaa tgaaataaag agaataattta ttcattggcg 5640
 ttaattaaat tatttgccta acttaagaaa actactgtgc gtaactctca gtttgtgctt 5700
 aactccattt gacatgaggt gacagaagag agtctgagtc tacctgtgga atatgttggt 5760
 ttattttcag tgcttgaaga tacattcaca aatacttggt ttgggaagac accgtttaat 5820
 ttaagttaa cttgcatgtt gtaaatgcgt tttatgttta aataaagagg aaaatttttt 5880
 gaaatgtaaa aaaaaaaaaa aaaaa 5905

<210> 30
 <211> 963
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> kinesin-1 heavy chain (NP_004512.1)

<400> 30

Met Ala Asp Leu Ala Glu Cys Asn Ile Lys Val Met Cys Arg Phe Arg
1 5 10 15

Pro Leu Asn Glu Ser Glu Val Asn Arg Gly Asp Lys Tyr Ile Ala Lys
20 25 30

Phe Gln Gly Glu Asp Thr Val Val Ile Ala Ser Lys Pro Tyr Ala Phe
35 40 45

Asp Arg Val Phe Gln Ser Ser Thr Ser Gln Glu Gln Val Tyr Asn Asp
50 55 60

Cys Ala Lys Lys Ile Val Lys Asp Val Leu Glu Gly Tyr Asn Gly Thr
65 70 75 80

Ile Phe Ala Tyr Gly Gln Thr Ser Ser Gly Lys Thr His Thr Met Glu
85 90 95

Gly Lys Leu His Asp Pro Glu Gly Met Gly Ile Ile Pro Arg Ile Val
100 105 110

JPOXMLDOC01-seq1

Gln Asp Ile Phe Asn Tyr Ile Tyr Ser Met Asp Glu Asn Leu Glu Phe
115 120 125

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

Leu Leu Asp Val Ser Lys Thr Asn Leu Ser Val His Glu Asp Lys Asn
145 150 155 160

Arg Val Pro Tyr Val Lys Gly Cys Thr Glu Arg Phe Val Cys Ser Pro
165 170 175

Asp Glu Val Met Asp Thr Ile Asp Glu Gly Lys Ser Asn Arg His Val
180 185 190

Ala Val Thr Asn Met Asn Glu His Ser Ser Arg Ser His Ser Ile Phe
195 200 205

Leu Ile Asn Val Lys Gln Glu Asn Thr Gln Thr Glu Gln Lys Leu Ser
210 215 220

Gly Lys Leu Tyr Leu Val Asp Leu Ala Gly Ser Glu Lys Val Ser Lys
225 230 235 240

Thr Gly Ala Glu Gly Ala Val Leu Asp Glu Ala Lys Asn Ile Asn Lys
245 250 255

Ser Leu Ser Ala Leu Gly Asn Val Ile Ser Ala Leu Ala Glu Gly Ser
260 265 270

Thr Tyr Val Pro Tyr Arg Asp Ser Lys Met Thr Arg Ile Leu Gln Asp
275 280 285

Ser Leu Gly Gly Asn Cys Arg Thr Thr Ile Val Ile Cys Cys Ser Pro
290 295 300

Ser Ser Tyr Asn Glu Ser Glu Thr Lys Ser Thr Leu Leu Phe Gly Gln
305 310 315 320

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

Ala Glu Gln Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys Asn Lys
340 345 350

Ile Leu Arg Asn Thr Ile Gln Trp Leu Glu Asn Glu Leu Asn Arg Trp
355 360 365

Arg Asn Gly Glu Thr Val Pro Ile Asp Glu Gln Phe Asp Lys Glu Lys
370 375 380

JPOXMLDOC01-seq1

Ala Asn Leu Glu Ala Phe Thr Val Asp Lys Asp Ile Thr Leu Thr Asn
385 390 395 400

Asp Lys Pro Ala Thr Ala Ile Gly Val Ile Gly Asn Phe Thr Asp Ala
405 410 415

Glu Arg Arg Lys Cys Glu Glu Glu Ile Ala Lys Leu Tyr Lys Gln Leu
420 425 430

Asp Asp Lys Asp Glu Glu Ile Asn Gln Gln Ser Gln Leu Val Glu Lys
435 440 445

Leu Lys Thr Gln Met Leu Asp Gln Glu Glu Leu Leu Ala Ser Thr Arg
450 455 460

Arg Asp Gln Asp Asn Met Gln Ala Glu Leu Asn Arg Leu Gln Ala Glu
465 470 475 480

Asn Asp Ala Ser Lys Glu Glu Val Lys Glu Val Leu Gln Ala Leu Glu
485 490 495

Glu Leu Ala Val Asn Tyr Asp Gln Lys Ser Gln Glu Val Glu Asp Lys
500 505 510

Thr Lys Glu Tyr Glu Leu Leu Ser Asp Glu Leu Asn Gln Lys Ser Ala
515 520 525

Thr Leu Ala Ser Ile Asp Ala Glu Leu Gln Lys Leu Lys Glu Met Thr
530 535 540

Asn His Gln Lys Lys Arg Ala Ala Glu Met Met Ala Ser Leu Leu Lys
545 550 555 560

Asp Leu Ala Glu Ile Gly Ile Ala Val Gly Asn Asn Asp Val Lys Gln
565 570 575

Pro Glu Gly Thr Gly Met Ile Asp Glu Glu Phe Thr Val Ala Arg Leu
580 585 590

Tyr Ile Ser Lys Met Lys Ser Glu Val Lys Thr Met Val Lys Arg Cys
595 600 605

Lys Gln Leu Glu Ser Thr Gln Thr Glu Ser Asn Lys Lys Met Glu Glu
610 615 620

Asn Glu Lys Glu Leu Ala Ala Cys Gln Leu Arg Ile Ser Gln His Glu
625 630 635 640

Ala Lys Ile Lys Ser Leu Thr Glu Tyr Leu Gln Asn Val Glu Gln Lys
645 650 655

JPOXMLDOC01-seq1

Lys Arg Gln Leu Glu Glu Ser Val Asp Ala Leu Ser Glu Glu Leu Val
 660 665 670
 Gln Leu Arg Ala Gln Glu Lys Val His Glu Met Glu Lys Glu His Leu
 675 680 685
 Asn Lys Val Gln Thr Ala Asn Glu Val Lys Gln Ala Val Glu Gln Gln
 690 695 700
 Ile Gln Ser His Arg Glu Thr His Gln Lys Gln Ile Ser Ser Leu Arg
 705 710 715 720
 Asp Glu Val Glu Ala Lys Ala Lys Leu Ile Thr Asp Leu Gln Asp Gln
 725 730 735
 Asn Gln Lys Met Met Leu Glu Gln Glu Arg Leu Arg Val Glu His Glu
 740 745 750
 Lys Leu Lys Ala Thr Asp Gln Glu Lys Ser Arg Lys Leu His Glu Leu
 755 760 765
 Thr Val Met Gln Asp Arg Arg Glu Gln Ala Arg Gln Asp Leu Lys Gly
 770 775 780
 Leu Glu Glu Thr Val Ala Lys Glu Leu Gln Thr Leu His Asn Leu Arg
 785 790 795 800
 Lys Leu Phe Val Gln Asp Leu Ala Thr Arg Val Lys Lys Ser Ala Glu
 805 810 815
 Ile Asp Ser Asp Asp Thr Gly Gly Ser Ala Ala Gln Lys Gln Lys Ile
 820 825 830
 Ser Phe Leu Glu Asn Asn Leu Glu Gln Leu Thr Lys Val His Lys Gln
 835 840 845
 Leu Val Arg Asp Asn Ala Asp Leu Arg Cys Glu Leu Pro Lys Leu Glu
 850 855 860
 Lys Arg Leu Arg Ala Thr Ala Glu Arg Val Lys Ala Leu Glu Ser Ala
 865 870 875 880
 Leu Lys Glu Ala Lys Glu Asn Ala Ser Arg Asp Arg Lys Arg Tyr Gln
 885 890 895
 Gln Glu Val Asp Arg Ile Lys Glu Ala Val Arg Ser Lys Asn Met Ala
 900 905 910
 Arg Arg Gly His Ser Ala Gln Ile Ala Lys Pro Ile Arg Pro Gly Gln
 915 920 925

JPOXMLDOC01-seq1

His Pro Ala Ala Ser Pro Thr His Pro Ser Ala Ile Arg Gly Gly Gly
930 935 940

Ala Phe Val Gln Asn Ser Gln Pro Val Ala Val Arg Gly Gly Gly Gly
945 950 955 960

Lys Gln Val

<210> 31
<211> 5842
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> CCDC6 (NM_005436.4)

<400> 31
agtgaatac tgcccaagcc cgggcggggt ctctgttctc tggcagagga ggtcccttgg 60
cagcgggaag cgccctctct ttctctcgcc gccgctccga gtctgcgccc tgggtgccagg 120
cgctcagctc ggcgctcccc tgtgctcgcc cggcgccac tcattcgag cccggccttc 180
gtcgccgccg cctccctgct gctcctctc ctttccccag cccgccgcgg ccatggcgga 240
cagcgccagc gagagcgaca cggacggggc ggggggcaac agcagcagct cggccgccat 300
gcagtcgtcc tgctcgctga cctcgggcgg cggcggtggc ggcgggggag gcggcggcgg 360
tgggaagtcg gggggcattg tcattctgcc gttccgcctg gaggagctca ccaaccgcct 420
ggcctcgctg cagcaagaga acaagggtgct gaagatagag ctggagacct acaaactgaa 480
gtgcaaggca ctgcaggagg agaaccgcga cctgcgcaaa gccagcgtga ccatccaagc 540
cagggtgag caggaagaag aattcattag taacacttta ttcaagaaaa ttcaggcttt 600
gcagaaggag aaagaaaccc ttgctgtaaa ttatgagaaa gaagaagaat tcctcactaa 660
tgagctctcc agaaaattga tgcagttgca gcatgagaaa gccgaactag aacagcatct 720
tgaacaagag caggaatttc aggtcaacaa actgatgaag aaaattaaaa aactggagaa 780
tgacaccatt tctaagcaac ttacattaga acagttgaga cgggagaaga ttgacctga 840
aaatacattg gaacaagaac aagaagcact agttaatcgc ctctggaaaa ggatggataa 900
gcttgaagct gaaaagcgaa tcctgcagga aaaattagac cagcccgtct ctgctccacc 960
atcgccatga gatattctcca tggagattga ttctccagaa aatatgatgc gtcacatcag 1020
gtttttaaag aatgaagtgg aacggctgaa gaagcaactg agagctgctc agttacagca 1080
ttcagagaaa atggcacagt atctggagga ggaacgtcac atgagagaag agaacttgag 1140
gctccagagg aagctgcaga gggagatgga gagaagagaa gccctctgtc gacagctctc 1200
cgagagtgag tccagcttag aaatggacga cgaaaggat tttaatgaga tgtctgcaca 1260
aggattaaga cctcgactg tgtccagccc gatcccttac acaccttctc cgagttcaag 1320

JPOXMLDOC01-seq1

caggcctata	tcacctgggtc	tatcatatgc	aagtcacacg	gttggtttca	cgccaccaac	1380
ttcactgact	agagctggaa	tgtcttatta	caattccccg	ggtcttcacg	tgcagcacat	1440
gggaacatcc	catggtatca	caaggccttc	accacggaga	agcaacagtc	ctgacaaatt	1500
caaacggccc	acgccgcctc	catctcccaa	cacacagacc	ccagtccagc	cacctccgcc	1560
tccacctccg	ccacccatgc	agccccacggt	cccctcagca	gccacctcgc	agcctactcc	1620
ttcgcaacat	tcggcgcacc	cctcctccca	gccttaatgc	atgagcttag	tctgaatttc	1680
aagttgggac	tcattccaatg	gagccgtcta	ctcaacgcca	aaggcttcct	tctctggcat	1740
at ttggatat	gacttatttg	cactgagggt	atctaggctt	cactatccat	tgtgttgtaa	1800
atgtttgtca	gaaatgcagc	cagtgtttgtg	ggtctacaac	actaaccaga	cgactttttc	1860
catcagtgtt	ttacttgaat	cttcatgtac	gtccattccc	tggctggaac	cttcgctggt	1920
tggattttgg	tatttcagca	gcagtgtgca	at ttttgctt	ggcccagagc	ttcattctcc	1980
tggcttttag	gtttgtaaaa	gaaaaaggga	tatctttttt	atattttttt	ccatgaatct	2040
gcagaaaatt	actgagctgt	tgttaccctc	ctctcattat	aatagtgttt	accaaacata	2100
ccaataattc	agcactacaa	ttcagacctt	tgaaaatctg	gctttcagtg	tagaacagaa	2160
agttagatga	atcagtgtcc	aagacatatt	ttctgtttta	cagaactttc	tacagataca	2220
ttttttacag	gttattttca	ttgtgttatt	gacatccatg	tctctcgtaa	aacagatggc	2280
ccaaagtaat	gaatcatgtg	gctgtacctt	ctccacataa	atgggatgga	taattatcgt	2340
atattaagat	gtgattctct	tttttatcct	taatgttaat	ctacttaacc	tggccccctc	2400
taacatgagt	cgataaatgt	tgtcctactc	accggtgggt	tcaatggcta	attagaatgt	2460
gttattttgat	ttctgctgca	gaaggcagtg	tgattgtaac	aaaaacaatg	cggcttcccc	2520
ctttcgtact	tcattttgtg	tctcttaaaa	tagagtttga	acaaatattt	taaagggtgca	2580
aaataccatt	agaaaatact	at ttgaaatg	gacattatcg	cattatcttg	gcataatggc	2640
cagaaaatat	tgtattgctt	ggcagaaaag	aaaataaggt	ctaaaggaaa	gtagcacatt	2700
agcattgatg	gctgttcatt	tcacccagta	taagcaagtg	cagtgtacaa	agaagtatat	2760
tctgaataca	ttattttccat	tcatttagca	caaataaatc	at ttggtttc	actttgcagt	2820
ggaacactga	gtcactcttt	tcttaacacg	tgcaacatct	taatttttgt	ttttcagcag	2880
ttgctgtttt	gtactttgggt	agtaaagtga	tttttaccac	ctgtgtttgc	atattttatat	2940
atgctgtgga	tgaaaataac	ttactagaga	atgtatatatt	tatgacaaga	atgtgtatct	3000
gttggaatata	atcagagaac	tgaaaagtaa	tttatcagta	at ttttaaga	gtccatgttt	3060
tgtgacaacc	atctctaata	gccaaactctt	tattaaacac	actcctaaaa	ataaggaacc	3120
atgacattgt	agatatttta	tattgtacag	tatagaaacc	tccatttttg	ccttcgaatg	3180
catattttaag	agttaacaga	atgaaaaaaa	aaagtcttgt	tggataatag	tgtttgacta	3240
gcgtttttaag	aacttgagag	taaaagcaac	aataagattt	tttcacctct	tcctgcttcc	3300
acccccaac	tgagaacatc	actcaattgt	ttggaagaaa	ctgtaggtct	atataaattt	3360

JPOXMLDOC01-seq1

tatttataat	gtatgtgtaa	tatacataat	cataatacag	ttctcagatg	caggggaagaa	3420
gtttggcatt	taatcattga	ggcttttaggt	ttttgatgtg	atcagactgg	gccatgtcaa	3480
acccggaatt	ttcaccaaca	gttcactcac	cctcctggtg	cattgccatt	ccaaggaatt	3540
ctgagagtag	gcaaacaaat	tttgccttca	tggtacagtt	ctcagttttt	cttataggag	3600
aaatatggta	tatgtttata	agaatctttt	atgagattat	agatttcaat	gctgtggata	3660
gtgtccttgca	cccaaacaag	aaagtccata	atggaatgat	cttccctcag	cttcctatcg	3720
atttagttac	ctcttgaaag	cacaaaaaatt	aaaacattgc	catatgttga	atttttaaaa	3780
agcacttgga	gtgagcgaac	atttcctgat	aaatgccttt	tagagatagg	ttcttgatat	3840
tcagacatct	gcagaaatgt	tctggttccc	aaagtcattt	cacttcgaaa	taaaacacag	3900
ctccttcaaa	cagcactttt	tccacataaa	tctagttgcc	tctccctgtg	gacattcaga	3960
actgatagaa	caaacactac	tcttttgaat	ttgatggttc	gtgtccttta	aagtgtttga	4020
ggacctatgc	agagcctgta	acacttgggt	agtacctgct	aggacaattt	cttggaatt	4080
gtcttactac	tagggatcag	taagatttag	attctgagcc	cataatggca	acagccccct	4140
cacctatggg	aagctgactt	ccctcagtcg	ggcacttctc	atgggggctg	aacatggttc	4200
ctgccattct	gttaccact	ctcccagggtg	agccctggat	tggctcccag	aaggcctttg	4260
taaaatcagt	agccgtcctg	caggcagggtg	ggagcaacag	gggcttcagt	agcttcattt	4320
tcctgtcttg	cagacagaga	cccttggtta	ccactgtgct	gctaatagga	taagtactct	4380
gttgccagat	taccatgcct	tttatacaaa	accaaattaa	cttaccta	acctgacacc	4440
tctttgggct	ctgaactgct	ttctctcatc	aagcatgcta	gcactctaga	cagaattcta	4500
gaaatttggc	agatagtggg	agcctttaat	tgaacttact	ccttcgttga	ctgaaaggag	4560
ttttaaatc	tgagctcctg	agatactgac	tagcaaccat	ggaatgaatg	tgtgaccaga	4620
aagtggcttt	gacaccaagt	gctactgtcc	ctttgtaatt	ggcttcta	agaattcaac	4680
cagaaataat	tgataatgtg	aatttttgtt	aattgttcac	ttgtaggaaa	atagaacatg	4740
tatcacctt	tgttaggtag	acatgaactt	ttcctgcaca	aagccttgct	tttagagaat	4800
gccaataag	gcaagaaaaa	gcatagtaac	ttgtgctttg	agagctcaat	atgtgtatct	4860
tatcagtaca	gaagaaatat	ttctgtgtaa	cttgatcttc	tgtctagtac	ttgtcttata	4920
ggtaaccaac	actgaaaact	ttgtagtgat	gactaccaa	gaaatacata	gtaaaacaac	4980
cttttatttc	caaattgtta	aagagccagc	cattgatgct	gctacatgag	ttccatgctc	5040
aagagccatt	gtaagagatt	aaggggtttc	taggtttttg	gtgatttttt	gtttgttttt	5100
ttctttgttt	tttagggttt	ttttttcttc	tttaattttt	tgattaaaa	atacacacag	5160
ctgttagcat	aaagtcgtgg	ggggcatttt	ctggaatgct	cagcagttct	gattaactgc	5220
caagcccagg	ttgcctctca	tgaggcaact	gaaaaaatcc	tgtgtcttga	tagcatgggt	5280
gctgtgtgtg	tgcatgtgtg	tgtctgcatt	catgccttaa	ctcgggttac	tgacaactt	5340
tagttcttga	cttagtctgc	accgtcatct	agattgtatt	gtacatctcg	gtctgaactt	5400

JPOXMLDOC01-seq1

catcctggca aaaacaaagt tgcaggcaca acagttttaag aatgcattcc tccagaagag	5460
tatctgggtca ggttgacccc tgagccttct ttggacttga tttggaactt agcctggaaa	5520
gcgaaagtgg actgtccaac agaaagatgt caacaaggaa aagaggagag ccaagcgcta	5580
gcatgccttt tgcctctgca tatctgtgca cactgtatgt tgttcatgat agcttgtcta	5640
caacttgact aggttggagt tctggtaata gtggcaatct tgacattctt ggtcagagtt	5700
tagagagatg taagactttc aattaatgtc ttatttactc ctttatgttg attagtcctt	5760
gatacatgtg ctgaatcaga aacctaaata aagataattt tttaaaatgt acctcttgag	5820
ccttaaaaaa aaaaaaaaaa aa	5842

<210> 32
 <211> 474
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CCDC6 (NP_005427.2)

<400> 32

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

JPOXMLDOC01-seq1

Gln His Leu Glu Gln Glu Gln Glu Phe Gln Val Asn Lys Leu Met Lys
165 170 175

Lys Ile Lys Lys Leu Glu Asn Asp Thr Ile Ser Lys Gln Leu Thr Leu
180 185 190

Glu Gln Leu Arg Arg Glu Lys Ile Asp Leu Glu Asn Thr Leu Glu Gln
195 200 205

Glu Gln Glu Ala Leu Val Asn Arg Leu Trp Lys Arg Met Asp Lys Leu
210 215 220

Glu Ala Glu Lys Arg Ile Leu Gln Glu Lys Leu Asp Gln Pro Val Ser
225 230 235 240

Ala Pro Pro Ser Pro Arg Asp Ile Ser Met Glu Ile Asp Ser Pro Glu
245 250 255

Asn Met Met Arg His Ile Arg Phe Leu Lys Asn Glu Val Glu Arg Leu
260 265 270

Lys Lys Gln Leu Arg Ala Ala Gln Leu Gln His Ser Glu Lys Met Ala
275 280 285

Gln Tyr Leu Glu Glu Glu Arg His Met Arg Glu Glu Asn Leu Arg Leu
290 295 300

Gln Arg Lys Leu Gln Arg Glu Met Glu Arg Arg Glu Ala Leu Cys Arg
305 310 315 320

Gln Leu Ser Glu Ser Glu Ser Ser Leu Glu Met Asp Asp Glu Arg Tyr
325 330 335

Phe Asn Glu Met Ser Ala Gln Gly Leu Arg Pro Arg Thr Val Ser Ser
340 345 350

Pro Ile Pro Tyr Thr Pro Ser Pro Ser Ser Ser Arg Pro Ile Ser Pro
355 360 365

Gly Leu Ser Tyr Ala Ser His Thr Val Gly Phe Thr Pro Pro Thr Ser
370 375 380

Leu Thr Arg Ala Gly Met Ser Tyr Tyr Asn Ser Pro Gly Leu His Val
385 390 395 400

Gln His Met Gly Thr Ser His Gly Ile Thr Arg Pro Ser Pro Arg Arg
405 410 415

Ser Asn Ser Pro Asp Lys Phe Lys Arg Pro Thr Pro Pro Pro Ser Pro
420 425 430

JPOXMLDOC01-seq1

Asn Thr Gln Thr Pro Val Gln Pro Pro Pro Pro Pro Pro Pro Pro Pro
435 440 445

Met Gln Pro Thr Val Pro Ser Ala Ala Thr Ser Gln Pro Thr Pro Ser
450 455 460

Gln His Ser Ala His Pro Ser Ser Gln Pro
465 470

<210> 33
<211> 3748
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> NCOA4 variant 1 (NM_001145260.1)

<400> 33
agagggcagt caagggcttc tggctgaccc gagcggagat ctcgcgagac tgtcagacgt 60
atggcgagag gtgtgggagg aagatttgtt tgtcgcgaga actctgcctt tgggccgtag 120
gttagtgttg ggccgtgtct cagtccaccc aaggctctct cggatcgctt ggagaggcac 180
tcggacctgt tatgtctgga cacattgctt caacatagaa cgcacatgaa caatgtggag 240
gtctaggctg gaatgggggc ccagttgacc acttttgctc tagctggagc agtgaggaga 300
atgaatacct tccaagacca gagtggcagc tccagtaata gagaaccctt tttgaggtgt 360
agtgatgcac ggagggactt ggagcttgct attggtggag ttctccgggc tgaacagcaa 420
attaaagata acttgcgaga ggtcaaagct cagattcaca gttgcataag ccgtcacctg 480
gaatgtctta gaagccgtga ggtatggctg tatgaacagg tggaccttat ttatcagctt 540
aaagaggaga cacttcaaca gcaggctcag cagctctact cgttattggg ccagttcaat 600
tgtcttactc atcaactgga gtgtacccaa aacaaagatc tagccaatca agtctctgtg 660
tgcctggaga gactgggcag tttgaccctt aagcctgaag attcaactgt cctgctcttt 720
gaagctgaca caattactct gcgccagacc atcaccacat ttgggtctct caaaaccatt 780
caaattcctg agcacttgat ggctcatgct agttcagcaa atattgggccc cttcctggag 840
aagagaggct gtatctccat gccagagcag aagtcagcat ccggtattgt agctgtccct 900
ttcagcgaat ggctccttgg aagcaaacct gccagtgggt atcaagctcc ttacataccc 960
agcaccgacc ccaggactg gcttacccaa aagcagacct tggagaacag tcagacttct 1020
tccagagcct gcaatttctt caataatgtc gggggaaacc taaagggtt agaaaactgg 1080
ctcctcaaga gtgaaaaatc aagttatcaa aagtgtaca gccattccac tactagttct 1140
ttctccattg aaatggaaaa ggttgagat caagagctt ctgatcaaga tgagatggac 1200
ctatcagatt ggctagtgc tccccaggaa tcccataagc tgcggaagcc tgagaatggc 1260
agtcgtgaaa ccagtgagaa gtttaagctc ttattccagt cctataatgt gaatgattgg 1320

JPOXMLDOC01-seq1

cttgtcaaga	ctgactcctg	taccaactgt	cagggaaacc	agcccaaagg	tgtggagatt	1380
gaaaacctgg	gcaatctgaa	gtgcctgaat	gaccacttgg	aggccaagaa	accattgtcc	1440
acccccagca	tggttacaga	ggattggctt	gtccagaacc	atcaggaccc	atgtaaggta	1500
gaggaggtgt	gcagagccaa	tgagccctgc	acaagctttg	cagagtgtgt	gtgtgatgag	1560
aattgtgaga	aggaggctct	gtataagtgg	cttctgaaga	aagaaggaaa	ggataaaaat	1620
gggatgcctg	tggaacccaa	acctgagcct	gagaagcata	aagattccct	gaatatgtgg	1680
ctctgtccta	gaaaagaagt	aatagaacaa	actaaagcac	caaaggcaat	gactccttct	1740
agaattgctg	attccttcca	agtcataaag	aacagcccct	tgtcggagtg	gcttatcagg	1800
cccccataca	aagaaggaag	tcccaaggaa	gtgcctggta	ctgaagacag	agctggcaaa	1860
cagaagttaa	aaagccccat	gaatacttcc	tggtgttcct	ttaacacagc	tgactgggtc	1920
ctgccaggaa	agaagatggg	caacctcagc	cagttatctt	ctggagaaga	caagtggctg	1980
cttcgaaaga	aggcccagga	agtattactt	aattcacctc	tacaggagga	acataacttc	2040
ccccagacc	attatggcct	ccctgcagtt	tgtgatctct	ttgcctgtat	gcagcttaaa	2100
gttgataaag	agaagtgggt	atatcgaact	cctctacagg	catacttcaa	aatgaacttt	2160
caagatgtaa	ccgttgggaa	ttttcagatc	ccatgtggat	tctagtagtt	tatataccta	2220
cctcgaagat	gtgaaggaat	ggacaagagt	tgagcagcct	ttctgctgat	tatcacacat	2280
catgagctga	gtgactgcag	cttgccaaat	ctttgtgttt	ctgggtctga	ccaattagct	2340
tagttcttct	cctgcctaata	tttgaactag	taaagcaaag	tgagtcatca	gattatgagt	2400
tactgtttta	aagaaaaatg	ctgtttattc	atgctgaggt	gattcagttc	cctccttctt	2460
acagaagtat	tttaattcac	cccacactag	aaatgcagca	tctttgtgga	cgtctttttc	2520
acaagcctcc	aaggctcctt	agattgggtc	gttactaaaa	gtacattaaa	acactcttgt	2580
ttatcgaagt	atattgatgt	attctaaagc	tagtaaactt	ccctaacgtt	taattgccct	2640
acagatgctt	ctcttgctgt	gggttttctt	ttgttagtgg	tctgaaataa	ttattttcct	2700
gttctattaa	tacatagtgt	attttgcaca	aaaaaattaa	cctgggtcaat	agtgattacc	2760
aaaatatata	ttaataatct	tggcaatttt	tgacattaat	tatgaaacat	tttagcccac	2820
gtagtttcta	cattattctt	cacttaaact	cagctactgc	aaattttgtc	tttctgtaaa	2880
tgttattaaa	atatccagtg	agctcttttag	aaggactcag	tattattttca	agactatttt	2940
tgaggtaatt	ctagcctttt	aaaatattct	acagacctac	ggggcttaaa	agaaccccag	3000
taccgactaa	gcaaataggc	aaaagacatg	ttggaaatgt	agtatagtac	ttgaaacagt	3060
cactatcata	gggataattg	gtgcatcctg	tgtaaatgga	agctgagctt	gacacctggt	3120
gcttttaagt	agggataaag	tcatcctctc	actgcaagca	cagcatacct	gtacctccaa	3180
aagtgacgtt	ttagtgaaca	ggccgttttc	aacacttggt	ccttgggggtg	ttcattgaag	3240
ctttgtgaaa	actactgatg	ttttctcagt	ctccttaaag	ttacgtccat	gctttaaaat	3300
gtctgtgtag	gagagaagtg	gggtttataa	tgttttctct	aagatatctt	tgctgctttc	3360

JPOXMLDOC01-seq1

cagactttga aactattaag cttcttaact gcctcttacc ggaaatactt ctgggggaaac	3420
ttcatgggtcc caaaatgtca ttgccatata gcttcactag agttctttga accacagctg	3480
aaaagagctt tgtattatTT tTTaattccc tccccagata tcatttagga gtattatata	3540
aaggtgggtgg gcaaaaacaa tgtaaggagc ctttccagtt atcttgagtt gcagctctgt	3600
agtttcttga ggccaaacac actgtatTTT acaagtcaaa atataattta cattaatcac	3660
tatgttaatg agtatgtaaa acattctTTT gcattgatga atTTTgtatc tgcttccatt	3720
aaaagcataa cagccataaa aaaaaaaa	3748

<210> 34
 <211> 3659
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> NCOA4 variant 2 (NM_001145261.1)

<400> 34	
agagggcagt caagggcttc tggctgaccc gagcggagat ctgcgcgagac tgtcagacgt	60
atggcgagag gtgtgggagg aagattgtgt tgtcgcgaga actctgcctt tggggccgtag	120
gtagtgttg ggccgtgtct cagtccaccc aaggtctcct cggatcgcct ggagaggcac	180
tcggacctgt tatgtctgga cacattgctt caacatagaa cgcacatgaa caatgtggag	240
gtctaggctg gaatgggggc ccagttgacc acttttgctc tagctggagc agtgaggaga	300
atgaatacct tccaagacca gagtggcagc tccagtaata gagaaccctt tttgagggtgt	360
agtgatgcac ggagggactt ggagcttgct attggtggag ttctccgggc tgaacagcaa	420
attaaagata acttgcgaga ggtcaaagct cagattcaca gttgcataag ccgtcacctg	480
gaatgtctta gaagccgtga ggtatggctg tatgaacagg tggaccttat ttatcagctt	540
aaagaggaga cacttcaaca gcaggctcag cagctctact cgttattggg ccagttcaat	600
tgtcttactc atcaactgga gtgtacccaa aacaaagatc tagccaatca agtctctgtg	660
tgcctggaga gactgggcag tttgaccctt aagcctgaag attcaactgt cctgctcttt	720
gaagctgaca caattactct gcgccagacc atcaccacat ttgggtctct caaaaccatt	780
caaattcctg agcacttgat ggctcatgct agttcagcaa atattggggc cttcctggag	840
aagagaggct gtatctccat gccagagcag aagtcagcat ccggtattgt agctgtccct	900
ttcagcgaat ggctccttgg aagcaaacct gccagtgggt atcaagctcc ttacataccc	960
agcaccgacc cccaggactg gcttacccaa aagcagacct tggagaacag tcagacttct	1020
tccagagcct gcaatttctt caataatgtc gggggaaacc taaagggtt agaaaactgg	1080
ctcctcaaga gtgaaaaatc aagttatcaa aagtgtaca gccattccac tactagttct	1140
ttctccattg aaatggaaaa gggttgagat caagagcttc ctgatcaaga tgagatggac	1200
ctatcagatt ggctagtgac tccccaggaa tcccataagc tgcggaagcc tgagaatggc	1260

JPOXMLDOC01-seq1

agtcgtgaaa	ccagtgagaa	gtttaagctc	ttattccagt	cctataatgt	gaatgattgg	1320
cttgtcaaga	ctgactcctg	taccaactgt	cagggaaacc	agcccaaagg	tgtggagatt	1380
gaaaacctgg	gcaatctgaa	gtgcctgaat	gaccacttgg	aggccaagaa	accattgtcc	1440
acccccagca	tggttacaga	ggattggctt	gtccagaacc	atcaggaccc	atgtaaggta	1500
gaggagggtgt	gcagagccaa	tgagccctgc	acaagctttg	cagagtgtgt	gtgtgatgag	1560
aattgtgaga	aggaggctct	gtataagtgg	cttctgaaga	aagaaggaaa	ggataaaaat	1620
gggatgcctg	tggaacccaa	acctgagcct	gagaagcata	aagattccct	gaatatgtgg	1680
ctctgtccta	gaaaagaagt	aatagaacaa	actaaagcac	caaaggcaat	gactccttct	1740
agaattgctg	attccttcca	agtcataaag	aacagcccct	tgtcggagtg	gcttatcagg	1800
cccccataca	aagaaggaag	tccaaggaa	gtgcctggta	ctgaagacag	agctggcaaa	1860
cagaagttta	aaagcccat	gaatacttcc	tggtgttcct	ttaacacagc	tgactgggtc	1920
ctgccaggaa	agaagatggg	caacctcagc	cagttatctt	ctggagaaga	caagtggctg	1980
cttcgaaaga	aggcccagga	agtattactt	aattcacctc	tacaggagga	acataacttc	2040
ccccagacc	attatggcct	ccctgcagtt	tgtgatctct	ttgcctgtat	gcagcttaaa	2100
gttgataaag	agaagtgggt	atatcgaact	cctctacaga	tgtgaaggaa	tggacaagag	2160
ttgagcagcc	tttctgctga	ttatcacaca	tcatgagctg	agtgactgca	gcttgccaaa	2220
tctttgtgtt	tctgggtctg	accaattagc	ttagttcttc	tcctgcctaa	ttttgaacta	2280
gtaaagcaaa	gtgagtcatc	agattatgag	ttactgttta	aaagaaaaat	gctgtttatt	2340
catgctgagg	tgattcagtt	ccctccttct	tacagaagta	ttttaattca	ccccacacta	2400
gaaatgcagc	atctttgtgg	acgtcttttt	cacaagcctc	caaggctcct	tagattgggt	2460
cgttactaaa	agtacattaa	aacactcttg	tttatcgaag	tatattgatg	tattctaaag	2520
ctagtaaact	tccctaacgt	ttaattgccc	tacagatgct	tctcttgctg	tgggttttct	2580
tttgtttagtg	gtctgaaata	attattttcc	tgttctatta	atacatagtg	tattttgcac	2640
aaaaaaatta	acctggtcaa	tagtgattac	caaaatatat	attaataatc	ttggcaattt	2700
ttgacattaa	ttatgaaaca	ttttagccca	cgttagttct	acattattct	tcacttaaac	2760
tcagctactg	caaattttgt	ctttctgtaa	atgttattaa	aatatccagt	gagctcttta	2820
gaaggactca	gtattatttc	aagactatft	ttgaggtaat	tctagccttt	taaaatattc	2880
tacagaccta	cggggcttaa	aagaacccca	gtaccgacta	agcaaatagg	caaaagacat	2940
gttggaatg	tagtatagta	cttgaaacag	tcactatcat	agggataatt	ggtgcatcct	3000
gtgtaaattg	aagctgagct	tgacacctgg	tgcttttaag	tagggataaa	gtcatcctct	3060
cactgcaagc	acagcatacc	tgtacctcca	aaagtgacgt	tttagtgaac	aggccgtttt	3120
caacacttgt	gccttggggg	gttcattgaa	gctttgtgaa	aactactgat	gttttctcag	3180
tctccttaaa	gttacgtcca	tgctttaaaa	tgtctgtgta	ggagagaagt	ggggtttata	3240
atgttttctc	taagatatct	ttgctgcttt	ccagactttg	aaactattaa	gcttcttaac	3300

JPOXMLDOC01-seq1

tgccctcttac	cggaataact	tctggggaaa	cttcatgggc	ccaaaatgtc	attgccatac	3360
agcttcacta	gagttctttg	aaccacagct	gaaaagagct	ttgtattatt	ttttaattcc	3420
ctccccagat	atcatttagg	agtattatat	aaaggtgggtg	ggcaaaaaca	atgtaaggag	3480
cctttccagt	tatcttgagt	tgcagctctg	tagtttcttg	aggccaaaca	cactgtattt	3540
tacaagtcaa	aatataat	acattaatca	ctatgttaat	gagtatgtaa	aacattcttt	3600
tgcatgtatg	aattttgtat	ctgcttccat	taaaagcata	acagccataa	aaaaaaaaa	3659

<210> 35
 <211> 3588
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> NCOA4 variant 3 (NM_001145262.1)

<400> 35						
attgattcaa	ttttacactg	tgccaggcat	tgtggcattc	cacacaaatg	gtgagaagct	60
aaaagtgaga	aatttggcac	aggtgaagaa	ggctgggtaa	cacatttgaa	agactgctaa	120
acaggtcttg	catgactggc	ctaagtcaa	agtgaagcag	cccatcacgc	tccagctctc	180
caaatcggag	ccggcatttc	acccatgtga	tacaggagca	gtgaggagaa	tgaatacctt	240
ccaagaccag	agtggcagct	ccagtaatag	agaaccctt	ttgaggtgta	gtgatgcacg	300
gagggacttg	gagcttgcta	ttggtggagt	tctccgggct	gaacagcaaa	ttaaagataa	360
cttgcgagag	gtcaaagctc	agattcacag	ttgcataagc	cgtcacctgg	aatgtcttag	420
aagccgtgag	gtatggctgt	atgaacaggt	ggaccttatt	tatcagctta	aagaggagac	480
acttcaacag	caggctcagc	agctctactc	gttattgggc	cagttcaatt	gtcttactca	540
tcaactggag	tgtacccaaa	acaaagatct	agccaatcaa	gtctctgtgt	gcctggagag	600
actgggcagt	ttgaccctta	agcctgaaga	ttcaactgtc	ctgctctttg	aagctgacac	660
aattactctg	cgccagacca	tcaccacatt	tgggtctctc	aaaaccattc	aaattcctga	720
gcacttgatg	gctcatgcta	gttcagcaaa	tattgggcc	ttcctggaga	agagaggctg	780
tatctccatg	ccagagcaga	agtcagcatc	cggtattgta	gctgtccctt	tcagcgaatg	840
gctccttgga	agcaaacctg	ccagtgggta	tcaagctcct	tacataccca	gcaccgaccc	900
ccaggactgg	cttaccctaa	agcagacctt	ggagaacagt	cagacttctt	ccagagcctg	960
caatttcttc	aataatgtcg	ggggaaacct	aaagggctta	gaaaactggc	tcctcaagag	1020
tgaaaaatca	agttatcaaa	agtgtaacag	ccattccact	actagttctt	tctccattga	1080
aatggaaaag	gttgagatc	aagagcttcc	tgatcaagat	gagatggacc	tatcagattg	1140
gctagtgact	ccccaggaat	cccataagct	gcggaagcct	gagaatggca	gtcgtgaaac	1200
cagtgagaag	tttaagctct	tattccagtc	ctataatgtg	aatgattggc	ttgtcaagac	1260
tgactcctgt	accaactgtc	agggaaacca	gcccaaaggt	gtggagattg	aaaacctggg	1320

JPOXMLDOC01-seq1

caatctgaag	tgctgaatg	accacttgga	ggccaagaaa	ccattgtcca	ccccagcat	1380
ggttacagag	gattggcttg	tccagaacca	tcaggacca	tgtaaggtag	aggagggtgtg	1440
cagagccaat	gagccctgca	caagctttgc	agagtgtgtg	tgtgatgaga	attgtgagaa	1500
ggaggctctg	tataagtggc	ttctgaagaa	agaaggaaag	gataaaaatg	ggatgcctgt	1560
ggaacccaaa	cctgagcctg	agaagcataa	agattccctg	aatatgtggc	tctgtcctag	1620
aaaagaagta	atagaacaaa	ctaaagcacc	aaaggcaatg	actccttcta	gaattgctga	1680
ttccttccaa	gtcataaaga	acagccccct	gtcggagtgg	cttatcaggc	ccccatacaa	1740
agaaggaagt	ccaaggaag	tgcttggtac	tgaagacaga	gctggcaaac	agaagtttaa	1800
aagccccatg	aatacttctt	ggtgttcctt	taacacagct	gactgggtcc	tgccaggaaa	1860
gaagatgggc	aacctcagcc	agttatcttc	tggagaagac	aagtggctgc	ttcgaaagaa	1920
ggcccaggaa	gtattactta	attcacctct	acaggaggaa	cataacttcc	ccccagacca	1980
ttatggcctc	cctgcagttt	gtgatctctt	tgctgtatg	cagcttaaag	ttgataaaga	2040
gaagtggtta	tatcgaactc	ctctacagat	gtgaaggaat	ggacaagagt	tgagcagcct	2100
ttctgctgat	tatcacacat	catgagctga	gtgactgcag	cttgccaaat	ctttgtgttt	2160
ctgggtctga	ccaattagct	tagttcttct	cctgcctaata	tttgaactag	taaagcaaag	2220
tgagtcatca	gattatgagt	tactgtttaa	aagaaaaatg	ctgtttattc	atgctgaggt	2280
gattcagttc	cctccttctt	acagaagtat	tttaattcac	cccacactag	aaatgcagca	2340
tctttgtgga	cgtctttttc	acaagcctcc	aaggctcctt	agattgggtc	gttactaaaa	2400
gtacattaaa	acactcttgt	ttatcgaagt	atattgatgt	attctaaagc	tagtaaactt	2460
ccctaacgtt	taattgccct	acagatgctt	ctcttgctgt	gggttttctt	ttgttagtgg	2520
tctgaaataa	ttattttctt	gttctattaa	tacatagtgt	attttgcaca	aaaaaattaa	2580
cctggccaat	agtgattacc	aaaatatata	ttaataatct	tggcaatttt	tgacattaat	2640
tatgaaacat	tttagccac	gttagttcta	cattattctt	cacttaaact	cagctactgc	2700
aaattttgtc	tttctgtaaa	tgttattaaa	atatccagt	agctcttttag	aaggactcag	2760
tattatttca	agactatttt	tgaggtaatt	ctagcctttt	aaaatattct	acagacctac	2820
ggggcttaaa	agaacccag	taccgactaa	gcaaataggc	aaaagacatg	ttggaaatgt	2880
agtatagtac	ttgaaacagt	cactatcata	gggataattg	gtgcatcctg	tgtaaattgga	2940
agctgagctt	gacacctggt	gcttttaagt	agggataaag	tcatcctctc	actgcaagca	3000
cagcatacct	gtacctcaa	aagtgacgtt	ttagtgaaca	ggccgttttc	aacacttggtg	3060
ccttgggggtg	ttcattgaag	ctttgtgaaa	actactgatg	ttttctcagt	ctccttaaag	3120
ttacgtccat	gctttaaaat	gtctgtgtag	gagagaagt	gggtttataa	tgttttctct	3180
aagatatctt	tgctgctttc	cagactttga	aactattaag	cttcttaact	gcctcttacc	3240
ggaaataactt	ctggggaaac	ttcatgggtcc	caaatgtca	ttgccataca	gcttcactag	3300
agttctttga	accacagctg	aaaagagctt	tgtattattt	tttaattccc	tccccagata	3360

JPOXMLDOC01-seq1

tcatttagga gtattatata aaggtggtgg gcaaaaacaa tgtaaggagc ctttccagtt	3420
atcttgagtt gcagctctgt agtttcttga ggccaaacac actgtatttt acaagtcaaa	3480
atataattta cattaatcac tatgttaatg agtatgtaaa acattctttt gcattgatga	3540
attttgtatc tgcttccatt aaaagcataa cagccataaa aaaaaaaa	3588

<210> 36
 <211> 3562
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> NCOA4 variant 4 (NM_001145263.1)

<400> 36	
agagggcagt caagggcttc tggctgaccc gagcggagat ctcgcgagac tgtcagacgt	60
atggcgagag gtgtgggagg aagattgtgt tgtcgcgaga actctgcctt tgggccgtag	120
gtagtggtgg ggccgtgtct cagtccaccc aaggtctcct cggatcgcct ggagaggcac	180
tcggacctgg agcagtgagg agaatgaata cttccaaga ccagagtggc agctccagta	240
atagagaacc ctttttgagg tgtagtgatg cacggaggga cttggagctt gctattggtg	300
gagttctccg ggctgaacag caaattaaag ataacttgcg agaggtcaaa gctcagattc	360
acagttgcat aagccgtcac ctggaatgtc ttagaagccg tgaggtatgg ctgtatgaac	420
aggtggacct tatttatcag cttaaagagg agacacttca acagcaggct cagcagctct	480
actcgttatt gggccagttc aattgtctta ctcatcaact ggagtgtacc caaaacaaag	540
atctagccaa tcaagtctct gtgtgcctgg agagactggg cagtttgacc cttaagcctg	600
aagattcaac tgtcctgctc tttgaagctg acacaattac tctgcgccag accatcacca	660
catttggttc tctcaaaacc attcaaattc ctgagcactt gatggctcat gctagttcag	720
caaataattg gcccttcctg gagaagagag gctgtatctc catgccagag cagaagtcag	780
catccggtat tgtagctgtc ctttccagcg aatggctcct tggaagcaaa cctgccagtg	840
gttatcaagc tccttacata cccagcaccg acccccagga ctggcttacc caaaagcaga	900
ccttgagaaa cagtcagact tcttccagag cctgcaattt cttcaataat gtcgggggaa	960
acctaaaggg cttagaaaac tggctcctca agagtgaaaa atcaagttat caaaagtgtg	1020
acagccattc cactactagt tctttctcca ttgaaatgga aaaggttgga gatcaagagc	1080
ttcctgatca agatgagatg gacctatcag attggctagt gactccccag gaatcccata	1140
agctgcggaa gcctgagaat ggcagtcgtg aaaccagtga gaagtttaag ctcttattcc	1200
agtcctataa tgtgaatgat tggcttgtca agactgactc ctgtaccaac tgtcagggaa	1260
accagcccaa aggtgtggag attgaaaacc tgggcaatct gaagtgcctg aatgaccact	1320
tggaggccaa gaaaccattg tccaccccca gcatggttac agaggattgg cttgtccaga	1380
accatcagga cccatgtaag gtagaggagg tgtgcagagc caatgagccc tgcacaagct	1440

JPOXMLDOC01-seq1

ttgcagagtg	tgtgtgtgat	gagaattgtg	agaaggaggc	tctgtataag	tggcttctga	1500
agaaagaagg	aaaggataaa	aatgggatgc	ctgtggaacc	caaacctgag	cctgagaagc	1560
ataaagattc	cctgaatatg	tggctctgtc	ctagaaaaga	agtaatagaa	caaactaaag	1620
caccaaaggc	aatgactcct	tctagaattg	ctgattcctt	ccaagtcata	aagaacagcc	1680
ccttgtcgga	gtggcttata	aggcccccat	acaaagaagg	aagtcccaag	gaagtgcctg	1740
gtactgaaga	cagagctggc	aaacagaagt	ttaaaagccc	catgaatact	tcctgggtgtt	1800
cctttaacac	agctgactgg	gtcctgccag	gaaagaagat	gggcaacctc	agccagttat	1860
cttctggaga	agacaagtgg	ctgcttcgaa	agaaggccca	ggaagtatta	cttaattcac	1920
ctctacagga	ggaacataac	ttccccccag	accattatgg	cctccctgca	gtttgtgatc	1980
tctttgcctg	tatgcagctt	aaagttgata	aagagaagtg	gttatatcga	actcctctac	2040
agatgtgaag	gaatggacaa	gagttgagca	gcctttctgc	tgattatcac	acatcatgag	2100
ctgagtgact	gcagcttgcc	aaatctttgt	gtttctgggt	ctgaccaatt	agcttagttc	2160
ttctcctgcc	taattttgaa	ctagtaaagc	aaagtgagtc	atcagattat	gagttactgt	2220
ttaaaagaaa	aatgctgttt	attcatgctg	aggtgattca	gttccctcct	tcttacagaa	2280
gtattttaat	tcaccccaca	ctagaaatgc	agcatctttg	tggaagtctt	tttcacaagc	2340
ctccaaggct	ccttagattg	ggcgttact	aaaagtacat	taaaacactc	ttgtttatcg	2400
aagtatatgg	atgtattcta	aagctagtaa	acttccctaa	cgtttaattg	ccctacagat	2460
gcttctcttg	ctgtgggttt	tcttttggtt	gtgggtctgaa	ataattatgt	tcctgttcta	2520
ttaatacata	gtgtattttg	cacaaaaaaa	ttaacctggg	caatagtgat	taccaaataa	2580
tatattaata	atcttggcaa	tttttgacat	taattatgaa	acatttttagc	ccacgttagt	2640
tctacattat	tcttcactta	aactcagcta	ctgcaaattt	tgtctttctg	taaatgttat	2700
taaaatatcc	agtgaagtct	ttagaaggac	tcagtattat	ttcaagacta	tttttgaggt	2760
aattctagcc	ttttaaaata	ttctacagac	ctacggggct	taaaagaacc	ccagtaccga	2820
ctaagcaaat	aggcaaaaga	catgttgga	atgtagtata	gtacttgaaa	cagtcactat	2880
catagggata	attggtgcat	cctgtgtaaa	tggaagctga	gcttgacacc	tggtgctttt	2940
aagtagggat	aaagtcattc	tctcactgca	agcacagcat	acctgtacct	ccaaaagtga	3000
cgtttttagt	aacaggccgt	tttcaacact	tgtgccttgg	gggtgttcatt	gaagctttgt	3060
gaaaactact	gatgttttct	cagtctcctt	aaagttacgt	ccatgcttta	aaatgtctgt	3120
gtaggagaga	agtgggggtt	ataatgtttt	ctctaagata	tctttgctgc	tttccagact	3180
ttgaaactat	taagcttctt	aactgcctct	taccggaaat	acttctgggg	aaacttcatg	3240
gtcccaaaat	gtcattgcca	tacagcttca	ctagagtctt	ttgaaccaca	gctgaaaaga	3300
gctttgtatt	attttttaat	tccctcccca	gatatcattt	aggagtatta	tataaagggtg	3360
gtgggcaaaa	acaatgtaag	gagcctttcc	agttatcttg	agttgcagct	ctgtagtttc	3420
ttgaggccaa	acacactgta	ttttacaagt	caaaatataa	tttacattaa	tcactatggt	3480

JPOXMLDOC01-seq1
aatgagtatg taaaacattc ttttgcattg atgaattttg tatctgcttc cattaaaagc 3540
ataacagcca taaaaaaaaa aa 3562

<210> 37
<211> 3502
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> NCOA4 variant 5 (NM_005437.3)

<400> 37
gaactggagt tgccgtgtga cgcgtgggcg ggacgaggcc cgggctcggg gacctttcgc 60
actcgggtca ggggtaaagc agcctgtcgc ttgccgggca gctggtgagt cgggtgacctg 120
gcctgtgagg agcagtgagg agaatgaata ccttccaaga ccagagtggc agctccagta 180
atagagaacc ctttttgagg tgtagtgatg cacggaggga cttggagctt gctattggtg 240
gagttctccg ggctgaacag caaattaaag ataacttgcg agagggtcaaa gctcagattc 300
acagttgcat aagccgtcac ctggaatgtc ttagaagccg tgagggtatgg ctgtatgaac 360
agggtggacct tattttatcag cttaaagagg agacacttca acagcaggct cagcagctct 420
actcgttatt gggccagttc aattgtctta ctcatcaact ggagtgtacc caaaacaaag 480
atctagccaa tcaagtctct gtgtgcctgg agagactggg cagtttgacc cttaagcctg 540
aagattcaac tgtcctgctc tttgaagctg acacaattac tctgcgccag accatcacca 600
catttggtgc tctcaaaacc attcaaattc ctgagcactt gatggctcat gctagttcag 660
caaataattg gcccttcctg gagaagagag gctgtatctc catgccagag cagaagtcag 720
catccggtat tgtagctgtc cctttcagcg aatggctcct tggaagcaaa cctgccagtg 780
gttatcaagc tccttacata cccagcaccg acccccagga ctggcttacc caaaagcaga 840
ccttgagaa cagtcagact tcttcagag cctgcaattt cttcaataat gtcgggggaa 900
acctaaaggg cttagaaaac tggctcctca agagtgaaaa atcaagttat caaaagtgtg 960
acagccattc cactactagt tctttctcca ttgaaatgga aaagggttga gatcaagagc 1020
ttcctgatca agatgagatg gacctatcag attggctagt gactccccag gaatcccata 1080
agctgcggaa gcctgagaat ggcagtcgtg aaaccagtga gaagtttaag ctcttattcc 1140
agtcctataa tgtgaatgat tggcttgtca agactgactc ctgtaccaac tgtcagggaa 1200
accagcccaa aggtgtggag attgaaaacc tgggcaatct gaagtgcctg aatgaccact 1260
tggaggccaa gaaaccattg tccaccccca gcatgggttac agaggattgg cttgtccaga 1320
accatcagga cccatgtaag gtagaggagg tgtgcagagc caatgagccc tgcacaagct 1380
ttgcagagtg tgtgtgtgat gagaattgtg agaaggaggc tctgtataag tggcttctga 1440
agaaagaagg aaaggataaa aatgggatgc ctgtggaacc caaacctgag cctgagaagc 1500
ataaagattc cctgaatatg tggctctgtc ctagaaaaga agtaatagaa caaactaaag 1560

JPOXMLDOC01-seq1

caccaaaggc	aatgactcct	tctagaattg	ctgattccct	ccaagtcata	aagaacagcc	1620
ccttgtcgga	gtggcttata	aggcccccat	acaaagaagg	aagtcccaag	gaagtgcctg	1680
gtactgaaga	cagagctggc	aaacagaagt	ttaaaagccc	catgaatact	tcctggtggt	1740
cctttaacac	agctgactgg	gtcctgccag	gaaagaagat	gggcaacctc	agccagttat	1800
cttctggaga	agacaagtgg	ctgcttcgaa	agaaggccca	ggaagtatta	cttaattcac	1860
ctctacagga	ggaacataac	ttccccccag	accattatgg	cctccctgca	gtttgtgatc	1920
tctttgcctg	tatgcagctt	aaagttgata	aagagaagtg	gttatatcga	actcctctac	1980
agatgtgaag	gaatggacaa	gagttgagca	gcctttctgc	tgattatcac	acatcatgag	2040
ctgagtgact	gcagcttgcc	aaatctttgt	gtttctgggt	ctgaccaatt	agcttagttc	2100
ttctcctgcc	taattttgaa	ctagtaaagc	aaagtgagtc	atcagattat	gagttactgt	2160
ttaaaagaaa	aatgctgttt	attcatgctg	agggtattca	gttccctcct	tcttacagaa	2220
gtattttaat	tcaccccaca	ctagaaatgc	agcatctttg	tggaagtctt	tttcacaagc	2280
ctccaaggct	ccttagattg	ggtcgttact	aaaagtacat	taaaacactc	ttgtttatcg	2340
aagtatatgg	atgtattcta	aagctagtaa	acttccctaa	cgtttaattg	ccctacagat	2400
gcttctcttg	ctgtggggtt	tcttttggtt	gtgggtctgaa	ataattatgt	tcctgttcta	2460
ttaatacata	gtgtattttg	cacaaaaaaa	ttaacctggg	caatagtgat	tacaaaaata	2520
tatattaata	atcttggcaa	tttttgacat	taattatgaa	acatttttagc	ccacgttagt	2580
tctacattat	tcttcactta	aactcagcta	ctgcaaattt	tgtctttctg	taaatgttat	2640
taaaatatcc	agtgaagtct	ttagaaggac	tcagtattat	ttcaagacta	tttttgaggt	2700
aattctagcc	ttttaaaata	ttctacagac	ctacggggct	taaaagaacc	ccagtaccga	2760
ctaagcaaat	aggcaaaaga	catgttgga	atgtagtata	gtacttgaaa	cagtcactat	2820
catagggata	attggtgcat	cctgtgtaaa	tggaagctga	gcttgacacc	tggtgctttt	2880
aagtagggat	aaagtcattc	tctcactgca	agcacagcat	acctgtacct	ccaaaagtga	2940
cgtttttagtg	aacaggccgt	tttcaacact	tgtgccttgg	gggtgttcatt	gaagctttgt	3000
gaaaactact	gatgttttct	cagtctcctt	aaagttacgt	ccatgcttta	aaatgtctgt	3060
gtaggagaga	agtgggggtt	ataatgtttt	ctctaagata	tctttgctgc	tttccagact	3120
ttgaaactat	taagcttctt	aactgcctct	taccggaaat	acttctgggg	aaacttcatg	3180
gtcccaaaat	gtcattgcca	tacagcttca	ctagagttct	ttgaaccaca	gctgaaaaga	3240
gctttgtatt	attttttaat	tccctcccca	gatattcatt	aggagtatta	tataaagggtg	3300
gtgggcaaaa	acaatgtaag	gagcctttcc	agttatcttg	agttgcagct	ctgtagtttc	3360
ttgaggccaa	acacactgta	ttttacaagt	caaaatataa	tttacattaa	tcactatggt	3420
aatgagtatg	taaaacattc	ttttgcattg	atgaattttg	tatctgcttc	cattaaaagc	3480
ataacagcca	taaaaaaaaa	aa				3502

JPOXMLDOC01-seq1

<211> 650
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> NCOA4 isoform 1 (NP_001138732.1)

<400> 38

Met Gly Ala Gln Leu Thr Thr Phe Ala Leu Ala Gly Ala Val Arg Arg
1 5 10 15

Met Asn Thr Phe Gln Asp Gln Ser Gly Ser Ser Ser Asn Arg Glu Pro
20 25 30

Leu Leu Arg Cys Ser Asp Ala Arg Arg Asp Leu Glu Leu Ala Ile Gly
35 40 45

Gly Val Leu Arg Ala Glu Gln Gln Ile Lys Asp Asn Leu Arg Glu Val
50 55 60

Lys Ala Gln Ile His Ser Cys Ile Ser Arg His Leu Glu Cys Leu Arg
65 70 75 80

Ser Arg Glu Val Trp Leu Tyr Glu Gln Val Asp Leu Ile Tyr Gln Leu
85 90 95

Lys Glu Glu Thr Leu Gln Gln Gln Ala Gln Gln Leu Tyr Ser Leu Leu
100 105 110

Gly Gln Phe Asn Cys Leu Thr His Gln Leu Glu Cys Thr Gln Asn Lys
115 120 125

Asp Leu Ala Asn Gln Val Ser Val Cys Leu Glu Arg Leu Gly Ser Leu
130 135 140

Thr Leu Lys Pro Glu Asp Ser Thr Val Leu Leu Phe Glu Ala Asp Thr
145 150 155 160

Ile Thr Leu Arg Gln Thr Ile Thr Thr Phe Gly Ser Leu Lys Thr Ile
165 170 175

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

Pro Phe Leu Glu Lys Arg Gly Cys Ile Ser Met Pro Glu Gln Lys Ser
195 200 205

Ala Ser Gly Ile Val Ala Val Pro Phe Ser Glu Trp Leu Leu Gly Ser
210 215 220

Lys Pro Ala Ser Gly Tyr Gln Ala Pro Tyr Ile Pro Ser Thr Asp Pro
Page 104

JPOXMLDOC01-seq1

225 230 235 240

Gln Asp Trp Leu Thr Gln Lys Gln Thr Leu Glu Asn Ser Gln Thr Ser
245 250 255

Ser Arg Ala Cys Asn Phe Phe Asn Asn Val Gly Gly Asn Leu Lys Gly
260 265 270

Leu Glu Asn Trp Leu Leu Lys Ser Glu Lys Ser Ser Tyr Gln Lys Cys
275 280 285

Asn Ser His Ser Thr Thr Ser Ser Phe Ser Ile Glu Met Glu Lys Val
290 295 300

Gly Asp Gln Glu Leu Pro Asp Gln Asp Glu Met Asp Leu Ser Asp Trp
305 310 315 320

Leu Val Thr Pro Gln Glu Ser His Lys Leu Arg Lys Pro Glu Asn Gly
325 330 335

Ser Arg Glu Thr Ser Glu Lys Phe Lys Leu Leu Phe Gln Ser Tyr Asn
340 345 350

Val Asn Asp Trp Leu Val Lys Thr Asp Ser Cys Thr Asn Cys Gln Gly
355 360 365

Asn Gln Pro Lys Gly Val Glu Ile Glu Asn Leu Gly Asn Leu Lys Cys
370 375 380

Leu 385 Asn Asp His Leu 390 Glu Ala Lys Lys Pro 395 Leu Ser Thr Pro Ser Met 400

Val Thr Glu Asp Trp Leu Val Gln Asn His Gln Asp Pro Cys Lys Val
405 410 415

Glu Glu Val Cys Arg Ala Asn Glu Pro Cys Thr Ser Phe Ala Glu Cys
420 425 430

Val Cys Asp Glu Asn Cys Glu Lys Glu Ala Leu Tyr Lys Trp Leu Leu
435 440 445

Lys Lys Glu Gly Lys Asp Lys Asn Gly Met Pro Val Glu Pro Lys Pro
450 455 460

Glu Pro Glu Lys His Lys Asp Ser Leu Asn Met Trp Leu Cys Pro Arg
465 470 475 480

Lys Glu Val Ile Glu Gln Thr Lys Ala Pro Lys Ala Met Thr Pro Ser
485 490 495

Arg Ile Ala Asp Ser Phe Gln Val Ile Lys Asn Ser Pro Leu Ser Glu
Page 105

JPOXMLDOC01-seq1

500

505

510

Trp Leu Ile Arg Pro Pro Tyr Lys Glu Gly Ser Pro Lys Glu Val Pro
 515 520 525
 Gly Thr Glu Asp Arg Ala Gly Lys Gln Lys Phe Lys Ser Pro Met Asn
 530 535 540
 Thr Ser Trp Cys Ser Phe Asn Thr Ala Asp Trp Val Leu Pro Gly Lys
 545 550 555 560
 Lys Met Gly Asn Leu Ser Gln Leu Ser Ser Gly Glu Asp Lys Trp Leu
 565 570 575
 Leu Arg Lys Lys Ala Gln Glu Val Leu Leu Asn Ser Pro Leu Gln Glu
 580 585 590
 Glu His Asn Phe Pro Pro Asp His Tyr Gly Leu Pro Ala Val Cys Asp
 595 600 605
 Leu Phe Ala Cys Met Gln Leu Lys Val Asp Lys Glu Lys Trp Leu Tyr
 610 615 620
 Arg Thr Pro Leu Gln Ala Tyr Phe Lys Met Asn Phe Gln Asp Val Thr
 625 630 635 640
 Val Gly Asn Phe Gln Ile Pro Cys Gly Phe
 645 650

<210> 39
 <211> 630
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> NCOA4 isoform 2 (NP_001138733.1)

<400> 39

Met Gly Ala Gln Leu Thr Thr Phe Ala Leu Ala Gly Ala Val Arg Arg
 1 5 10 15
 Met Asn Thr Phe Gln Asp Gln Ser Gly Ser Ser Ser Asn Arg Glu Pro
 20 25 30
 Leu Leu Arg Cys Ser Asp Ala Arg Arg Asp Leu Glu Leu Ala Ile Gly
 35 40 45
 Gly Val Leu Arg Ala Glu Gln Gln Ile Lys Asp Asn Leu Arg Glu Val
 50 55 60
 Lys Ala Gln Ile His Ser Cys Ile Ser Arg His Leu Glu Cys Leu Arg

65

70

75

80

Ser Arg Glu Val Trp₈₅ Leu Tyr Glu Gln Val₉₀ Asp Leu Ile Tyr Gln₉₅ Leu

Lys Glu Glu Thr₁₀₀ Leu Gln Gln Gln Ala₁₀₅ Gln Gln Leu Tyr Ser₁₁₀ Leu Leu

Gly Gln Phe₁₁₅ Asn Cys Leu Thr His₁₂₀ Gln Leu Glu Cys Thr₁₂₅ Gln Asn Lys

Asp Leu₁₃₀ Ala Asn Gln Val Ser₁₃₅ Val Cys Leu Glu Arg₁₄₀ Leu Gly Ser Leu

Thr₁₄₅ Leu Lys Pro Glu Asp₁₅₀ Ser Thr Val Leu₁₅₅ Phe Glu Ala Asp Thr₁₆₀

Ile Thr Leu Arg Gln₁₆₅ Thr Ile Thr Thr Phe₁₇₀ Gly Ser Leu Lys Thr₁₇₅ Ile

Gln Ile Pro Glu₁₈₀ His Leu Met Ala His₁₈₅ Ala Ser Ser Ala Asn₁₉₀ Ile Gly

Pro Phe Leu₁₉₅ Glu Lys Arg Gly Cys₂₀₀ Ile Ser Met Pro Glu₂₀₅ Gln Lys Ser

Ala Ser₂₁₀ Gly Ile Val Ala Val₂₁₅ Pro Phe Ser Glu Trp₂₂₀ Leu Leu Gly Ser

Lys₂₂₅ Pro Ala Ser Gly Tyr₂₃₀ Gln Ala Pro Tyr Ile₂₃₅ Pro Ser Thr Asp Pro₂₄₀

Gln Asp Trp Leu Thr₂₄₅ Gln Lys Gln Thr Leu₂₅₀ Glu Asn Ser Gln Thr₂₅₅ Ser

Ser Arg Ala Cys₂₆₀ Asn Phe Phe Asn Asn₂₆₅ Val Gly Gly Asn Leu₂₇₀ Lys Gly

Leu Glu Asn₂₇₅ Trp Leu Leu Lys Ser₂₈₀ Glu Lys Ser Ser Tyr₂₈₅ Gln Lys Cys

Asn Ser₂₉₀ His Ser Thr Thr Ser₂₉₅ Ser Phe Ser Ile Glu₃₀₀ Met Glu Lys Val

Gly₃₀₅ Asp Gln Glu Leu Pro₃₁₀ Asp Gln Asp Glu Met₃₁₅ Asp Leu Ser Asp Trp₃₂₀

Leu Val Thr Pro Gln₃₂₅ Glu Ser His Lys Leu₃₃₀ Arg Lys Pro Glu Asn₃₃₅ Gly

Ser Arg Glu Thr Ser Glu Lys Phe Lys Leu Leu Phe Gln Ser Tyr Asn

JPOXMLDOC01-seq1

340

345

350

Val Asn Asp Trp Leu Val Lys Thr Asp Ser Cys Thr Asn Cys Gln Gly
 355 360 365
 Asn Gln Pro Lys Gly Val Glu Ile Glu Asn Leu Gly Asn Leu Lys Cys
 370 375 380
 Leu Asn Asp His Leu Glu Ala Lys Lys Pro Leu Ser Thr Pro Ser Met
 385 390 395 400
 Val Thr Glu Asp Trp Leu Val Gln Asn His Gln Asp Pro Cys Lys Val
 405 410 415
 Glu Glu Val Cys Arg Ala Asn Glu Pro Cys Thr Ser Phe Ala Glu Cys
 420 425 430
 Val Cys Asp Glu Asn Cys Glu Lys Glu Ala Leu Tyr Lys Trp Leu Leu
 435 440 445
 Lys Lys Glu Gly Lys Asp Lys Asn Gly Met Pro Val Glu Pro Lys Pro
 450 455 460
 Glu Pro Glu Lys His Lys Asp Ser Leu Asn Met Trp Leu Cys Pro Arg
 465 470 475 480
 Lys Glu Val Ile Glu Gln Thr Lys Ala Pro Lys Ala Met Thr Pro Ser
 485 490 495
 Arg Ile Ala Asp Ser Phe Gln Val Ile Lys Asn Ser Pro Leu Ser Glu
 500 505 510
 Trp Leu Ile Arg Pro Pro Tyr Lys Glu Gly Ser Pro Lys Glu Val Pro
 515 520 525
 Gly Thr Glu Asp Arg Ala Gly Lys Gln Lys Phe Lys Ser Pro Met Asn
 530 535 540
 Thr Ser Trp Cys Ser Phe Asn Thr Ala Asp Trp Val Leu Pro Gly Lys
 545 550 555 560
 Lys Met Gly Asn Leu Ser Gln Leu Ser Ser Gly Glu Asp Lys Trp Leu
 565 570 575
 Leu Arg Lys Lys Ala Gln Glu Val Leu Leu Asn Ser Pro Leu Gln Glu
 580 585 590
 Glu His Asn Phe Pro Pro Asp His Tyr Gly Leu Pro Ala Val Cys Asp
 595 600 605
 Leu Phe Ala Cys Met Gln Leu Lys Val Asp Lys Glu Lys Trp Leu Tyr

610

615

620

Arg Thr Pro Leu Gln Met
625 630

<210> 40
<211> 614
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> NCOA4 isoform 3 (NP_001138734.1)

<400> 40

Met Asn Thr Phe Gln Asp Gln Ser Gly Ser Ser Ser Asn Arg Glu Pro
1 5 10 15

Leu Leu Arg Cys Ser Asp Ala Arg Arg Asp Leu Glu Leu Ala Ile Gly
20 25 30

Gly Val Leu Arg Ala Glu Gln Gln Ile Lys Asp Asn Leu Arg Glu Val
35 40 45

Lys Ala Gln Ile His Ser Cys Ile Ser Arg His Leu Glu Cys Leu Arg
50 55 60

Ser Arg Glu Val Trp Leu Tyr Glu Gln Val Asp Leu Ile Tyr Gln Leu
65 70 75 80

Lys Glu Glu Thr Leu Gln Gln Gln Ala Gln Gln Leu Tyr Ser Leu Leu
85 90 95

Gly Gln Phe Asn Cys Leu Thr His Gln Leu Glu Cys Thr Gln Asn Lys
100 105 110

Asp Leu Ala Asn Gln Val Ser Val Cys Leu Glu Arg Leu Gly Ser Leu
115 120 125

Thr Leu Lys Pro Glu Asp Ser Thr Val Leu Leu Phe Glu Ala Asp Thr
130 135 140

Ile Thr Leu Arg Gln Thr Ile Thr Thr Phe Gly Ser Leu Lys Thr Ile
145 150 155 160

Gln Ile Pro Glu His Leu Met Ala His Ala Ser Ser Ala Asn Ile Gly
165 170 175

Pro Phe Leu Glu Lys Arg Gly Cys Ile Ser Met Pro Glu Gln Lys Ser
180 185 190

Ala Ser Gly Ile Val Ala Val Pro Phe Ser Glu Trp Leu Leu Gly Ser
Page 109

195

200

205

Lys Pro Ala Ser Gly Tyr Gln Ala Pro Tyr Ile Pro Ser Thr Asp Pro
 210 215 220

Gln Asp Trp Leu Thr Gln Lys Gln Thr Leu Glu Asn Ser Gln Thr Ser
 225 230 235 240

Ser Arg Ala Cys Asn Phe Phe Asn Asn Val Gly Gly Asn Leu Lys Gly
 245 250 255

Leu Glu Asn Trp Leu Leu Lys Ser Glu Lys Ser Ser Tyr Gln Lys Cys
 260 265 270

Asn Ser His Ser Thr Thr Ser Ser Phe Ser Ile Glu Met Glu Lys Val
 275 280 285

Gly Asp Gln Glu Leu Pro Asp Gln Asp Glu Met Asp Leu Ser Asp Trp
 290 295 300

Leu Val Thr Pro Gln Glu Ser His Lys Leu Arg Lys Pro Glu Asn Gly
 305 310 315 320

Ser Arg Glu Thr Ser Glu Lys Phe Lys Leu Leu Phe Gln Ser Tyr Asn
 325 330 335

Val Asn Asp Trp Leu Val Lys Thr Asp Ser Cys Thr Asn Cys Gln Gly
 340 345 350

Asn Gln Pro Lys Gly Val Glu Ile Glu Asn Leu Gly Asn Leu Lys Cys
 355 360 365

Leu Asn Asp His Leu Glu Ala Lys Lys Pro Leu Ser Thr Pro Ser Met
 370 375 380

Val Thr Glu Asp Trp Leu Val Gln Asn His Gln Asp Pro Cys Lys Val
 385 390 395 400

Glu Glu Val Cys Arg Ala Asn Glu Pro Cys Thr Ser Phe Ala Glu Cys
 405 410 415

Val Cys Asp Glu Asn Cys Glu Lys Glu Ala Leu Tyr Lys Trp Leu Leu
 420 425 430

Lys Lys Glu Gly Lys Asp Lys Asn Gly Met Pro Val Glu Pro Lys Pro
 435 440 445

Glu Pro Glu Lys His Lys Asp Ser Leu Asn Met Trp Leu Cys Pro Arg
 450 455 460

Lys Glu Val Ile Glu Gln Thr Lys Ala Pro Lys Ala Met Thr Pro Ser
 Page 110

465 JPOXMLDOC01-seq1 470 475 480

Trp Leu Ile Arg Pro Pro Tyr Lys Glu Gly Ser Pro Lys Glu Val Pro
500 505 510

Gly Thr Glu Asp Arg Ala Gly Lys Gln Lys Phe Lys Ser Pro Met Asn
515 520 525

Thr Ser Trp Cys Ser Phe Asn Thr Ala Asp Trp Val Leu Pro Gly Lys
530 535 540

Lys Met Gly Asn Leu Ser Gln Leu Ser Ser Gly Glu Asp Lys Trp Leu
545 550 555 560

Leu Arg Lys Lys Ala Gln Glu Val Leu Leu Asn Ser Pro Leu Gln Glu
565 570 575

Glu His Asn Phe Pro Pro Asp His Tyr Gly Leu Pro Ala Val Cys Asp
580 585 590

Leu Phe Ala Cys Met Gln Leu Lys Val Asp Lys Glu Lys Trp Leu Tyr
595 600 605

Arg Thr Pro Leu Gln Met
610

<210>	41
<211>	614
<212>	PRT
<213>	Homo sapiens

```
<220>
<221> misc_feature
<223> NCOA4 isoform 3 (NP_001138735.1)
```

<400> 41

Met Asn Thr Phe Gln Asp Gln Ser Gly Ser Ser Ser Asn Arg Glu Pro
1 5 10 15

Leu Leu Arg Cys Ser Asp Ala Arg Arg Asp Leu Glu Leu Ala Ile Gly
20 25 30

Gly Val Leu Arg Ala Glu Gln Gln Ile Lys Asp Asn Leu Arg Glu Val
35 40 45

Lys Ala Gln Ile His Ser Cys Ile Ser Arg His Leu Glu Cys Leu Arg
50 55 60

Ser Arg Glu Val Trp Leu Tyr Glu Gln Val Asp Leu Ile Tyr Gln Leu
Page 111

JPOXMLDOC01-seq1

65

70

75

80

Lys Glu Glu Thr Leu₈₅ Gln Gln Gln Ala Gln₉₀ Gln Leu Tyr Ser Leu₉₅ Leu

Gly Gln Phe Asn₁₀₀ Cys Leu Thr His Gln₁₀₅ Leu Glu Cys Thr Gln₁₁₀ Asn Lys

Asp Leu Ala₁₁₅ Asn Gln Val Ser Val₁₂₀ Cys Leu Glu Arg Leu₁₂₅ Gly Ser Leu

Thr Leu₁₃₀ Lys Pro Glu Asp Ser₁₃₅ Thr Val Leu Leu Phe₁₄₀ Glu Ala Asp Thr

Ile₁₄₅ Thr Leu Arg Gln Thr₁₅₀ Ile Thr Thr Phe Gly₁₅₅ Ser Leu Lys Thr Ile₁₆₀

Gln Ile Pro Glu His₁₆₅ Leu Met Ala His Ala₁₇₀ Ser Ser Ala Asn Ile₁₇₅ Gly

Pro Phe Leu Glu₁₈₀ Lys Arg Gly Cys Ile₁₈₅ Ser Met Pro Glu Gln₁₉₀ Lys Ser

Ala Ser Gly₁₉₅ Ile Val Ala Val Pro₂₀₀ Phe Ser Glu Trp Leu₂₀₅ Leu Gly Ser

Lys Pro₂₁₀ Ala Ser Gly Tyr Gln₂₁₅ Ala Pro Tyr Ile Pro₂₂₀ Ser Thr Asp Pro

Gln₂₂₅ Asp Trp Leu Thr Gln₂₃₀ Lys Gln Thr Leu Glu₂₃₅ Asn Ser Gln Thr Ser₂₄₀

Ser Arg Ala Cys Asn₂₄₅ Phe Phe Asn Asn Val₂₅₀ Gly Gly Asn Leu Lys₂₅₅ Gly

Leu Glu Asn Trp₂₆₀ Leu Leu Lys Ser Glu₂₆₅ Lys Ser Ser Tyr Gln₂₇₀ Lys Cys

Asn Ser His₂₇₅ Ser Thr Thr Ser Ser₂₈₀ Phe Ser Ile Glu Met₂₈₅ Glu Lys Val

Gly Asp₂₉₀ Gln Glu Leu Pro Asp₂₉₅ Gln Asp Glu Met Asp₃₀₀ Leu Ser Asp Trp

Leu₃₀₅ Val Thr Pro Gln Glu₃₁₀ Ser His Lys Leu Arg₃₁₅ Lys Pro Glu Asn Gly₃₂₀

Ser Arg Glu Thr Ser₃₂₅ Glu Lys Phe Lys Leu₃₃₀ Leu Phe Gln Ser Tyr₃₃₅ Asn

Val Asn Asp Trp Leu Val Lys Thr Asp Ser Cys Thr Asn Cys Gln Gly

JPOXMLDOC01-seq1

340

345

350

Asn Gln Pro Lys Gly Val Glu Ile Glu Asn Leu Gly Asn Leu Lys Cys
 355 360 365
 Leu Asn Asp His Leu Glu Ala Lys Lys Pro Leu Ser Thr Pro Ser Met
 370 375 380
 Val Thr Glu Asp Trp Leu Val Gln Asn His Gln Asp Pro Cys Lys Val
 385 390 395 400
 Glu Glu Val Cys Arg Ala Asn Glu Pro Cys Thr Ser Phe Ala Glu Cys
 405 410 415
 Val Cys Asp Glu Asn Cys Glu Lys Glu Ala Leu Tyr Lys Trp Leu Leu
 420 425 430
 Lys Lys Glu Gly Lys Asp Lys Asn Gly Met Pro Val Glu Pro Lys Pro
 435 440 445
 Glu Pro Glu Lys His Lys Asp Ser Leu Asn Met Trp Leu Cys Pro Arg
 450 455 460
 Lys Glu Val Ile Glu Gln Thr Lys Ala Pro Lys Ala Met Thr Pro Ser
 465 470 475 480
 Arg Ile Ala Asp Ser Phe Gln Val Ile Lys Asn Ser Pro Leu Ser Glu
 485 490 495
 Trp Leu Ile Arg Pro Pro Tyr Lys Glu Gly Ser Pro Lys Glu Val Pro
 500 505 510
 Gly Thr Glu Asp Arg Ala Gly Lys Gln Lys Phe Lys Ser Pro Met Asn
 515 520 525
 Thr Ser Trp Cys Ser Phe Asn Thr Ala Asp Trp Val Leu Pro Gly Lys
 530 535 540
 Lys Met Gly Asn Leu Ser Gln Leu Ser Ser Gly Glu Asp Lys Trp Leu
 545 550 555 560
 Leu Arg Lys Lys Ala Gln Glu Val Leu Leu Asn Ser Pro Leu Gln Glu
 565 570 575
 Glu His Asn Phe Pro Pro Asp His Tyr Gly Leu Pro Ala Val Cys Asp
 580 585 590
 Leu Phe Ala Cys Met Gln Leu Lys Val Asp Lys Glu Lys Trp Leu Tyr
 595 600 605
 Arg Thr Pro Leu Gln Met

610

<210> 42
 <211> 614
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> NCOA4 isoform 3 (NP_005428.1)

<400> 42

Met Asn Thr Phe Gln Asp Gln Ser Gly Ser Ser Ser Asn Arg Glu Pro
 1 5 10 15

Leu Leu Arg Cys Ser Asp Ala Arg Arg Asp Leu Glu Leu Ala Ile Gly
 20 25 30

Gly Val Leu Arg Ala Glu Gln Gln Ile Lys Asp Asn Leu Arg Glu Val
 35 40 45

Lys Ala Gln Ile His Ser Cys Ile Ser Arg His Leu Glu Cys Leu Arg
 50 55 60

Ser Arg Glu Val Trp Leu Tyr Glu Gln Val Asp Leu Ile Tyr Gln Leu
 65 70 75 80

Lys Glu Glu Thr Leu Gln Gln Gln Ala Gln Gln Leu Tyr Ser Leu Leu
 85 90 95

Gly Gln Phe Asn Cys Leu Thr His Gln Leu Glu Cys Thr Gln Asn Lys
 100 105 110

Asp Leu Ala Asn Gln Val Ser Val Cys Leu Glu Arg Leu Gly Ser Leu
 115 120 125

Thr Leu Lys Pro Glu Asp Ser Thr Val Leu Leu Phe Glu Ala Asp Thr
 130 135 140

Ile Thr Leu Arg Gln Thr Ile Thr Thr Phe Gly Ser Leu Lys Thr Ile
 145 150 155 160

Gln Ile Pro Glu His Leu Met Ala His Ala Ser Ser Ala Asn Ile Gly
 165 170 175

Pro Phe Leu Glu Lys Arg Gly Cys Ile Ser Met Pro Glu Gln Lys Ser
 180 185 190

Ala Ser Gly Ile Val Ala Val Pro Phe Ser Glu Trp Leu Leu Gly Ser
 195 200 205

Lys Pro Ala Ser Gly Tyr Gln Ala Pro Tyr Ile Pro Ser Thr Asp Pro
 Page 114

JPOXMLDOC01-seq1

210

215

220

Gln Asp Trp Leu Thr Gln Lys Gln Thr Leu Glu Asn Ser Gln Thr Ser
 225 230 235 240

Ser Arg Ala Cys Asn Phe Phe Asn Asn Val Gly Gly Asn Leu Lys Gly
 245 250 255

Leu Glu Asn Trp Leu Leu Lys Ser Glu Lys Ser Ser Tyr Gln Lys Cys
 260 265 270

Asn Ser His Ser Thr Thr Ser Ser Phe Ser Ile Glu Met Glu Lys Val
 275 280 285

Gly Asp Gln Glu Leu Pro Asp Gln Asp Glu Met Asp Leu Ser Asp Trp
 290 295 300

Leu Val Thr Pro Gln Glu Ser His Lys Leu Arg Lys Pro Glu Asn Gly
 305 310 315 320

Ser Arg Glu Thr Ser Glu Lys Phe Lys Leu Leu Phe Gln Ser Tyr Asn
 325 330 335

Val Asn Asp Trp Leu Val Lys Thr Asp Ser Cys Thr Asn Cys Gln Gly
 340 345 350

Asn Gln Pro Lys Gly Val Glu Ile Glu Asn Leu Gly Asn Leu Lys Cys
 355 360 365

Leu Asn Asp His Leu Glu Ala Lys Lys Pro Leu Ser Thr Pro Ser Met
 370 375 380

Val Thr Glu Asp Trp Leu Val Gln Asn His Gln Asp Pro Cys Lys Val
 385 390 395 400

Glu Glu Val Cys Arg Ala Asn Glu Pro Cys Thr Ser Phe Ala Glu Cys
 405 410 415

Val Cys Asp Glu Asn Cys Glu Lys Glu Ala Leu Tyr Lys Trp Leu Leu
 420 425 430

Lys Lys Glu Gly Lys Asp Lys Asn Gly Met Pro Val Glu Pro Lys Pro
 435 440 445

Glu Pro Glu Lys His Lys Asp Ser Leu Asn Met Trp Leu Cys Pro Arg
 450 455 460

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

Arg Ile Ala Asp Ser Phe Gln Val Ile Lys Asn Ser Pro Leu Ser Glu
 Page 115

Trp Leu Ile Arg Pro Pro Tyr Lys Glu Gly Ser Pro Lys Glu Val Pro
500 505 510

Gly Thr Glu Asp Arg Ala Gly Lys Gln Lys Phe Lys Ser Pro Met Asn
515 520 525

Thr Ser Trp Cys Ser Phe Asn Thr Ala Asp Trp Val Leu Pro Gly Lys
530 535 540

Lys Met Gly Asn Leu Ser Gln Leu Ser Ser Gly Glu Asp Lys Trp Leu
545 550 555 560

Leu Arg Lys Lys Ala Gln Glu Val Leu Leu Asn Ser Pro Leu Gln Glu
565 570 575

Glu His Asn Phe Pro Pro Asp His Tyr Gly Leu Pro Ala Val Cys Asp
580 585 590

Leu Phe Ala Cys Met Gln Leu Lys Val Asp Lys Glu Lys Trp Leu Tyr
595 600 605

Arg Thr Pro Leu Gln Met
610

<210> 43
<211> 8339
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> TRIM33 transcript variant a (NM_015906.3)

<400> 43
ctgcggctgg ggctgggggc ggcggcggcg gcgacgcggg cggcgggcgg cgcggggcgg 60
tccggcgggt tcaaagagga aaacatggcg gaaaacaaag gcggcggcga ggctgagagc 120
ggcggcgggg gcagcggcag cgcgccggtg actgccgggg ccgccgggccc cgccgcgcag 180
gaggcggagc cgcctctcac cgcggtgctg gtggaggagg aggaggagga aggcggcagg 240
gccggcgctg agggcggcgc ggccggggccc gacgacgggg ggggtggccgc ggcctcctcg 300
ggctcggccc aggtctgttc atctcctgcg gcctcagtgg gactggagt tgccgggggc 360
gcagtatcga cgccggctcc agctccagcc tcggctcccg ctccgggtcc ctcggcaggg 420
ccgcctcctg gaccgccagc ctgcctcctg gacacctgcg ccgtgtgtca gcagagcttg 480
cagagccggc gtgaggcgga gcccagctg ctgccctgtc ttacttcctt ctgcctgcgc 540
tgcctgcccg agccggagcg ccagctcagc gtgcccatcc cggggggcag caacggcgac 600
atccagcaag ttggtgtaat acggtgcccga gtatgccgcc aagaatgcag acagatagac 660

JPOXMLDOC01-seq1

cttgtggata	attatTTTTgt	gaaagacaca	tctgaagctc	ctagcagttc	tgatgaaaaa	720
tcagaacagg	tatgtactag	ttgtgaagac	aatgcaagtg	cagttggctt	ttgtgtagaa	780
tgtggagagt	ggctatgtaa	gacatgtatc	gaagcacatc	aaagagtaaa	atttactaaa	840
gatcacttga	tcaggaagaa	agaagatgtc	tcagagtctg	ttggagcatc	tgggtcaacgc	900
cctgttttct	gccctgtaca	caaacaagaa	cagttgaaac	ttttctgtga	aacatgtgat	960
agattgacat	gtagagactg	tcagctattg	gaacacaaaag	aacataggta	tcagtttttg	1020
gaagaagctt	ttcaaaatca	gaaggggtgca	attgagaatc	tactggcgaa	acttcttgag	1080
aagaagaatt	atgttcattt	tgcagctact	caggtgcaga	ataggataaa	agaagtaaatt	1140
gagactaaca	aacgagtaga	acaggaaatt	aaagtggcca	ttttcacctt	tatcaatgaa	1200
attaataaga	aaggaaaatc	tctcttaca	cagctagaga	atgttacaaa	ggaaagacag	1260
atgaagttac	tacagcagca	gaatgacatc	acaggccttt	cccggcaggt	gaagcatggt	1320
atgaacttca	caaattgggc	aattgcaagt	ggcagcagca	cagcactact	atacagcaag	1380
cgactgatta	ctttccagtt	gcgtcatatt	ttgaaagcac	ggtgtgatcc	tgtccctgct	1440
gctaattggag	caatacgttt	ccattgtgat	cccaccttct	gggcaaagaa	tgtagtcaat	1500
ttaggtaatc	tagtaataga	gagtaaacca	gctcctgggt	atactcctaa	tgttgtagtt	1560
gggcaagttc	ctccagggac	aaaccacatt	agtaaaaccc	ctggacagat	taacttagca	1620
cagcttcgac	tccagcacat	gcaacaacaa	gtatatgcac	agaaacatca	gcagttgcaa	1680
cagatgagga	tgcagcaacc	accagcacct	gtaccaacta	caacaacaac	aacacaacag	1740
catcctagac	aagcagcccc	tcagatgtta	caacaacagc	ctcctcgatt	gatcagtggtg	1800
caaacaatgc	aaagaggcaa	catgaactgt	ggagcttttc	aagcccatca	gatgagactg	1860
gctcagaatg	ctgccagaat	accaggggata	cccaggcaca	gcggccctca	atattccatg	1920
atgcagccac	acctccaaag	acaacactca	aaccaggggc	atgctggacc	ctttcccgtg	1980
gtatcggtac	acaacaccac	aatcaaccca	acgagcccta	ctacagcaac	tatggcaaatt	2040
gcaaaccgag	gtcccaccag	cccatctggt	acagcaatag	agctaattccc	ctcagttacc	2100
aatccagaaa	accttccatc	gctgccagat	attccacca	tacagttgga	agatgctggc	2160
tcaagtagtt	tagataatct	actaagtaga	tacatctcag	gcagtcacct	acccccacag	2220
cctacaagca	ccatgaatcc	ttctccaggt	ccctctgccc	tttctccggg	atcatcaggt	2280
ttatccaatt	ctcacacacc	tgtgagaccc	ccaagtactt	ctagtactgg	cagtcgaggc	2340
agctgtgggt	catcaggaag	aactgctgag	aagacaagtc	ttagtttcaa	atctgatcag	2400
gtgaagggtca	agcaagaacc	tgggactgaa	gatgaaatat	gtagcttttc	aggaggtgta	2460
aaacaagaaa	aaacagagga	tggcaggagg	agtgcttgca	tgttgagcag	tcctgagagt	2520
agcttgacac	cacctctctc	aaccaacctg	catctagaaa	gtgaattgga	tgcattggca	2580
agcctggaaa	accatgtgaa	aattgaacct	gcagatatga	atgaaagctg	caaacagtca	2640
gggctcagca	gccttggttaa	tggaaagtcc	ccaattcgaa	gcctcatgca	caggtcggca	2700

JPOXMLDOC01-seq1

aggattggag	gagatggcaa	caataaagat	gatgacccaa	atgaagactg	gtgtgctgtc	2760
tgccaaaacg	gaggagatct	cttgtgctgc	gaaaaatgtc	caaaggctct	tcatctaact	2820
tgtcatgttc	caacactact	tagctttcca	agtggggact	ggatatgcac	attttgtaga	2880
gatattggaa	agccagaagt	tgaatatgat	tgtgataatt	tgcaacatag	taagaagggg	2940
aaaactgcgc	aggggttaag	ccccgtggac	caaaggaaat	gtgaacgtct	tctgctttac	3000
ctctattgcc	atgaattaag	tattgaattc	caggagcctg	ttcctgcttc	gataccaaac	3060
tactataaaa	ttataaagaa	accaatggat	ttatccaccg	tgaaaaagaa	gcttcagaaa	3120
aaacattccc	aacactacca	aatcccggat	gactttgtgg	ccgatgtccg	tttgatcttc	3180
aagaactgtg	aaagggttaa	tgaaatgatg	aaagttgttc	aagtttatgc	agacacacaa	3240
gagattaatt	tgaaggctga	ttcagaagta	gctcaggcag	ggaaagcagt	tgcattgtac	3300
tttgaagata	aactcacaga	gatctactca	gacaggacct	tcgcaccttt	gccagagttt	3360
gagcaggaag	aggatgatgg	tgaggtaact	gaggactctg	atgaagactt	tatacagccc	3420
cgcagaaaac	gcctaaagtc	agatgagaga	ccagtacata	taaagtaaaa	tgacatggat	3480
ttaaatcaat	tgtttaaaaa	aaaaaaaaacg	aaaaaaaaaa	aaaaaacaca	aaaaacccag	3540
aaaactttta	agtgttgctg	gaatatcctg	cctacagtgg	gcacctcctt	gaagaagctg	3600
atagctttta	cacagtatta	gattgaaata	atggacagaa	acacattcct	gtcaagaaag	3660
ggggagagaa	gtctgtttgc	aagtttcaaa	gcaaaaagca	aaagtgaat	gatttgagga	3720
tttctgttct	aatggagatg	attctctgat	tgtagaaat	ggcaaataat	gatgattgtg	3780
tgctattgat	tggtgcagga	tacttggtat	acgagtaa	acttgagact	cgtgtcactt	3840
gataaat	ctttttggac	taggtcgcac	agttattaaa	acaactttta	accctcccc	3900
ttcacacaca	tacatatcag	gttggtttct	agttaaaaac	ccaagtagct	cagattctac	3960
tttaatgtca	gtgcagattt	gcattgaatc	atgccattat	gttttttctc	atttttatgc	4020
tgttgggtct	tagtttttaa	attgatataa	agaactcagc	aatggtttta	ttttctactc	4080
atacttaggg	tttaggaaac	actaccacta	gttatcattt	aatcaacttc	aatgggtctac	4140
tgaaacaaaa	atggtaactt	ttcattagtg	gattatttag	agttatagta	gttgtttcca	4200
gaaaacactt	cctcacaa	gtacttccca	atcaa	atcat	agttattccc	4260
atgaaaggca	gaatgtttgt	ttcaaaatta	atctagtttt	ctgtacattt	aaatttgaga	4320
aggtgacaac	tggtcttttt	ccagtcttcc	ttcatgtcag	ttttctgata	gaccactatt	4380
ggcaaacagt	atctgtcaac	taccaa	atgt	ctgtatttca	ctttgtctta	4440
tttgtaaata	gtgaactaaa	acttttggca	gatcagcaac	atgtgctgag	cctgtttttt	4500
aagcta	atgt	taatgttcct	atcaagaatg	gatttgtaat	atatgctgtc	4560
tatttcta	at	gttcacattc	atattttgag	gttctatctt	atttta	4620
tctcaaaaa	tcttcagaag	cagcttatta	ttgaaat	atc	gaaatattga	4680
gtgggggttag	attactcatc	tgtccaccaa	gtgggacatt	tgcattggact	gggggcttaa	4740

JPOXMLDOC01-seq1

aggacttaga	agagacctgt	aagtaaattcc	tgaaaatgag	ccaatcccca	cttgaatggt	4800
tactggagta	aaccacacctt	taccacccca	attacagcac	ccgaggccga	taaaccaact	4860
tggctctggt	tcatttttct	tttcttcatt	tgtgatgctc	agattcaaaa	tgtgtgttct	4920
acactgttac	aggcttctct	tttgtttgat	taaagatttt	agtcctactt	ttgtatggac	4980
acattagaat	attcagagac	caaaatagaa	gaatttgctg	ttagatat	ttcagaagtc	5040
agcagatttg	tggcaaatca	tttatttgcc	tttttaaaaa	ttcatttaag	cagttcagag	5100
agtagactac	tcagaaaatt	atttcacgta	attgtctaag	aggccaatat	tttttaatgc	5160
atattgaatc	aaataaagt	ctctaaagaa	attattatac	aaattccttt	gggttggttt	5220
tcttttctta	acaaggggtg	ggggtaaaca	ggaatatgat	tcaggctttc	tgggtgtgta	5280
tttaaagagt	attgatttta	ttattactat	tgatttactt	tattcctggc	ttccttttca	5340
cttttctttc	aatttttaaa	aaataattta	agccgttgaa	aatataccaa	actgttgaaa	5400
cattttactc	aaatttttaa	ttcctaataa	tgttttttta	taagaggag	aaaattattt	5460
aaaaatactt	atgcctatgc	caatttccct	ctttttcac	aaaatccatg	atttcagttt	5520
gtaagtagac	atatatctaa	gggcacattt	ttggaaagt	aggaatagca	gcagtataac	5580
ttcattttgt	caggcctttg	agttctaata	ttttgtattg	ctcttcaaat	ggatcctttt	5640
aaaaaaattg	tagataatga	gtcataaata	gattctgcca	actgagggga	gaaacatttt	5700
aagtaaatat	ttttcagtat	ttggggcctt	aaaaaataat	tgtgtttcct	taaaattaca	5760
tgtagatag	agtttttagg	tttttttggg	tttaagattg	gttaaagcaa	tttaaaagcc	5820
acttttttgt	caacatttaa	tagcctccac	ttctgttaag	ataatgtata	ctgctgagga	5880
attactatta	atagctatca	acataccacc	attaaattaa	ggtattcact	ttagattttt	5940
tattaaagct	tttttcttgc	acactgatcg	ttgtgtttct	aagctgattt	tttcagctct	6000
aatataccta	tggttaaaaa	gtataaaaac	ttaaattgat	atttagatat	atgttttcct	6060
attagtttat	gttttaaaaa	gacaaaattg	tatctgtcag	tccctgaagg	cagtttggtt	6120
ttatactctc	tcacatttgt	atttggtttt	taaatggcag	tatttttagaa	gatttgagaa	6180
aaagtccaca	taataatggt	ttcttaaaa	cttttaaa	gtttgctgta	cttcaattta	6240
cttcttccat	cagaaaacta	agaacaaagt	gttgctcagt	ctgttccgct	gacctaaatt	6300
tgtgttttca	gcacttggct	cagccaattc	actgagtga	ggaattgctt	tatgaggcaa	6360
agcatgtgaa	agttctaaag	tatgggttaga	ttgtaggctg	tgctctatat	ggaaacatca	6420
aaccattact	acagagaaat	gataaggcat	tggatccact	attgaaatta	ttatttttgg	6480
atcaacaagt	tggtactttc	tgacttctgt	atcttaacat	aagggaattt	taggtaatgc	6540
taagtcagtt	gtctcatttt	ttgtgataag	ttttggaatt	tttagttaat	tgaaataaat	6600
aatgctttta	aatagaagta	aaagggttat	aagtgtgcaa	attgtagatt	tatcaattac	6660
ctcagcaggt	atcctgccat	gtaattatta	gtgattagt	tttaataagat	aatagattca	6720
ggctttccaa	ctatgccctt	ggattgtggc	ctactgtatg	ttattaaatg	gtctcttact	6780

JPOXMLDOC01-seq1

atccaaaatg	ggagtagatg	ctgtggcccc	gtctcccttg	gcttttacgt	cccatatcca	6840
ccccattca	tgtacaacat	gtgaaatata	aaaatctcat	ttcttgtcaa	aatcagcact	6900
gcttatttgc	atactcagca	tcggatcagt	gagtagtttt	ataaaaaatc	cacgcaccca	6960
actcccttag	ttaaaacaga	ttcttaattc	ataccatgaa	ttcttaattt	ctgtaccatc	7020
tatgttaatg	atctgctgaa	ggtgactcaa	gattttcaag	gtgtaataca	gtttgatcat	7080
gtaccggacc	tggatattta	atTTTTTTTt	cctcacagtt	aatctcctcc	ttgataaagc	7140
aataacactg	ctttgagtct	gttgcctaata	agcatgtcag	aatcctctcc	tggatggtga	7200
ttttatagga	aagtttgtat	gcatatcacc	cagtctatct	tttaaaaatt	aagaaattta	7260
aatgtatgct	ggaagtaatg	acactatatt	gtggcatttt	atTTTTAAAA	ttggggaaag	7320
ttgcatattt	ttttaaaagt	aagtgtttga	gtaaaaaaat	tgaagggtact	tttttaagga	7380
aaaaaattta	tatgccacag	tttacataga	catttcagat	tcaacacgta	ctcttgaata	7440
taatgggttc	ttttacttgg	tcaaaatgca	tgtatagcat	ttctttcatc	ttagttcctt	7500
gtgtttgcct	atgtggctct	ttatatattt	tttattgtat	cgaagaaaca	aaactatctt	7560
caaaaataag	ttaatttgga	tatatattgtc	atatcaaact	acaaagtgtg	caaagttaag	7620
tttagccctt	ttctagaaag	tgatctttta	aattaaaaat	gctcctcttt	taaattcacc	7680
aaatttatgt	gtgggaaggc	accaaataga	ttttgtaagt	gccactgcaa	tattcccttt	7740
caagtgtggc	ctaaatttca	atcttaagga	tggaatgcat	gtctgtctct	tgttctgaaa	7800
aatgtaggca	tctactacat	tttaaaacac	agtgaacat	atacataagc	ctataaaaaa	7860
agatttgtgc	aatttgaaag	cctgttaatt	ttttatgtag	acatacctac	acacgaaagg	7920
gttaaattca	cagccttact	agttccttgc	ttccagtatt	tcaattgggtc	tcctcccttc	7980
attattatta	ttactactag	tactattatt	tttgcacata	gttaactgcc	cttcaatatg	8040
attcttaaaa	agtgtgtgtt	ctgtgggtatc	gtattctcta	aataatcata	tttaattttt	8100
taaaacaagg	ttgcagtttc	taattgtttc	gttcctgtgt	ttttgctggt	gtgtaataaa	8160
agcaagtttt	ttcttttcat	ggttatttta	tacattagct	gcctgtaaata	aattcttggt	8220
ataatgctct	ggaatgtgtt	gtagaagttg	tattagatta	gttttaaac	cttgtttgaa	8280
agccacattg	ttttggttat	ttctatttaa	ttagaaaatt	gaaaaagttt	tcaaatgaa	8339

<210> 44
 <211> 8288
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> TRIM33 transcript variant b (NM_033020.2)

<400>	44	
ctgcggctgg	ggctgggggc	ggcggcggcg gcgacgcggg cggcgggcgg cgcggggcgg 60
tccggcgggt	tcaaagagga	aaacatggcg gaaaacaaag gcggcggcga ggctgagagc 120

JPOXMLDOC01-seq1

ggcggcgggg	gcagcggcag	cgcgccggta	actgccgggg	ccgccggggc	cgccgcgcag	180
gaggcggagc	cgcctctcac	cgcggtgctg	gtggaggagg	aggaggagga	aggcggcagg	240
gccggcgctg	agggcgggcg	ggccggggcc	gacgacgggg	gggtggccgc	ggcctcctcg	300
ggctcggccc	aggctgcttc	atctcctgcg	gcctcagtgg	gcactggagt	tgccgggggc	360
gcagtatcga	cgccgggtcc	agctccagcc	tcgggtcccc	ctccgggtcc	ctcggcaggg	420
ccgcctcctg	gaccgccagc	ctcgctcctg	gacacctgcg	ccgtgtgtca	gcagagcttg	480
cagagccggc	gtgaggcgga	gcccagctg	ctgccctgtc	ttcactcctt	ctgcctgcgc	540
tgcctgcccc	agccggagcg	ccagctcagc	gtgcccattc	cggggggcag	caacggcgac	600
atccagcaag	ttggtgtaat	acggtgcccc	gtatgccgcc	agaatgcag	acagatagac	660
cttgtggata	attattttgt	gaaagacaca	tctgaagctc	ctagcagttc	tgatgaaaaa	720
tcagaacagg	tatgtactag	ttgtgaagac	aatgcaagtg	cagttggctt	ttgtgtagaa	780
tgtggagagt	ggctatgtaa	gacatgtatc	gaagcacatc	aaagagtaaa	atttactaaa	840
gatcacttga	tcaggaagaa	agaagatgtc	tcagagtctg	ttggagcatc	tggtcaacgc	900
cctgttttct	gccctgtaca	caaacaagaa	cagttgaaac	ttttctgtga	aacatgtgat	960
agattgacat	gtagagactg	tcagctattg	gaacacaaaag	aacataggta	tcagtttttg	1020
gaagaagctt	ttcaaaatca	gaagggtgca	attgagaatc	tactggcgaa	acttcttgag	1080
aagaagaatt	atgttcattt	tgcagctact	caggtgcaga	ataggataaa	agaagtaaatt	1140
gagactaaca	aacgagtaga	acaggaaatt	aaagtggcca	ttttcacctt	tatcaatgaa	1200
attaataaga	aaggaaaatc	tctcttaca	cagctagaga	atgttacaaa	ggaaagacag	1260
atgaagttac	tacagcagca	gaatgacatc	acaggccttt	cccggcaggt	gaagcatggt	1320
atgaacttca	caaattgggc	aattgcaagt	ggcagcagca	cagcactact	atacagcaag	1380
cgactgatta	ctttccagtt	gcgtcatatt	ttgaaagcac	ggtgtgatcc	tgtccctgct	1440
gctaattggag	caatacgttt	ccattgtgat	cccaccttct	gggcaaagaa	tgtagtcaat	1500
ttaggtaatc	tagtaataga	gagtaaacca	gctcctgggt	atactcctaa	tgttgtagtt	1560
gggcaagttc	ctccagggac	aaaccacatt	agtaaaacc	ctggacagat	taacttagca	1620
cagcttcgac	tccagcacat	gcaacaacaa	gtatatgcac	agaaacatca	gcagttgcaa	1680
cagatgagga	tgcagcaacc	accagcacct	gtaccaacta	caacaacaac	aacacaacag	1740
catcctagac	aagcagcccc	tcagatgtta	caacaacagc	ctcctcgatt	gatcagtggtg	1800
caaacaatgc	aaagaggcaa	catgaactgt	ggagcttttc	aagcccatca	gatgagactg	1860
gctcagaatg	ctgccagaat	accagggata	cccaggcaca	gcggccctca	atattccatg	1920
atgcagccac	acctccaaag	acaacactca	aaccaggggc	atgctggacc	ctttcccgtg	1980
gtatcggtac	acaacaccac	aatcaacca	acgagcccta	ctacagcaac	tatggcaaatt	2040
gcaaaccgag	gtcccaccag	cccatctgtt	acagcaatag	agctaattccc	ctcagttacc	2100
aatccagaaa	accttccatc	gctgccagat	attccacca	tacagttgga	agatgctggc	2160

JPOXMLDOC01-seq1

tcaagtagtt	tagataatct	actaagtaga	tacatctcag	gcagtcacct	acccccacag	2220
cctacaagca	ccatgaatcc	ttctccaggt	ccctctgccc	tttctccggg	atcatcaggt	2280
ttatccaatt	ctcacacacc	tgtgagaccc	ccaagtactt	ctagtactgg	cagtcgaggc	2340
agctgtgggt	catcaggaag	aactgctgag	aagacaagtc	ttagtttcaa	atctgatcag	2400
gtgaagggtca	agcaagaacc	tgggactgaa	gatgaaatat	gtagcttttc	aggagggtgta	2460
aaacaagaaa	aaacagagga	tggcaggagg	agtgttgca	tgttgagcag	tcctgagagt	2520
agcttgacac	cacctctctc	aaccaacctg	catctagaaa	gtgaattgga	tgcattggca	2580
agcctggaaa	accatgtgaa	aattgaacct	gcagatatga	atgaaagctg	caaacagtca	2640
gggctcagca	gccttgttaa	tggaaagtcc	ccaattcgaa	gcctcatgca	caggctcgga	2700
aggattggag	gagatggcaa	caataaagat	gatgacccaa	atgaagactg	gtgtgctgtc	2760
tgccaaaacg	gaggagatct	cttggtgctgc	gaaaaatgtc	caaagggtctt	tcattctaact	2820
tgtcatgttc	caacactact	tagctttcca	agtggggact	ggatatgcac	attttgtaga	2880
gatattggaa	agccagaagt	tgaatatgat	tgtgataatt	tgcaacatag	taagaagggg	2940
aaaactgcgc	aggggttaag	ccccgtggac	caaaggaaat	gtgaacgtct	tctgctttac	3000
ctctattgcc	atgaattaag	tattgaattc	caggagcctg	ttcctgcttc	gataccaaac	3060
tactataaaa	ttataaagaa	accaatggat	ttatccaccg	tgaaaaagaa	gcttcagaaa	3120
aaacattccc	aacactacca	aatcccggat	gactttgtgg	ccgatgtccg	tttgatcttc	3180
aagaactgtg	aaaggtttaa	tgaagctgat	tcagaagtag	ctcaggcagg	gaaagcagtt	3240
gcattgtact	ttgaagataa	actcacagag	atctactcag	acaggacctt	cgcacctttg	3300
ccagagtttg	agcaggaaga	ggatgatggg	gaggtaactg	aggactctga	tgaagacttt	3360
atacagcccc	gcagaaaacg	cctaaagtca	gatgagagac	cagtacatat	aaagtaaaat	3420
gacatggatt	taaatcaatt	gtttaaaaaa	aaaaaaacga	aaaaaaaaaa	aaaaacacaa	3480
aaaaccagca	aaacttttaa	gtgttgctgg	aatatcctgc	ctacagtggg	cacctccttg	3540
aagaagctga	tagcttttac	acagtattag	attgaaataa	tggacagaaa	cacattcttg	3600
tcaagaaagg	gggagagaag	tctgtttgca	agtttcaaag	caaaaagcaa	aagtgaaatg	3660
atttgaggat	ttctgttcta	atggagatga	ttctctgatt	gttagaaatg	gcaaattattg	3720
atgattgtgt	gctattgatt	gggtgcaggat	acttgggtata	cgagtaaata	cttgagactc	3780
gtgtcacttg	ataaattttc	tttttggtgact	aggtcgcaca	gttattaaaa	caacttttaa	3840
ccctccccct	tcacacacat	acatatcagg	ttgttttcta	gttaaaaacc	caagtagctc	3900
agattctact	ttaatgtcag	tgcagatttg	cattgaatca	tgccattatg	ttttttctca	3960
tttttatgct	gttgggtctt	agttttttaa	ttgatataaa	gaactcagca	atggttttat	4020
tttctactca	tacttagggg	ttaggaaaca	ctaccactag	ttatcattta	atcaacttca	4080
atggcttact	gaaacaaaaa	tggtaacttt	tcattagtgg	attattttaga	gttatagtag	4140
ttgtttccag	aaaacacttc	ctcacaattg	tacttcccaa	tcaaatcatg	tgatcataca	4200

JPOXMLDOC01-seq1

gttattccca	tgaaaggcag	aatgtttgtt	tcaaaattaa	tctagttttc	tgtacattta	4260
aatttgagaa	ggtgacaact	ggctcttttc	cagtcttcct	tcatgtcagt	tttctgatag	4320
accactattg	gcaaacagta	tctgtcaact	accaaagtgt	taaaattttc	tgtatttcac	4380
tttgtcttat	ttgtaaatag	tgaactaaaa	cttttggcag	atcagcaaca	tttgctgagc	4440
ctgtttttta	agctaattgt	tattcttact	aatgttccta	tcaagaatgg	atttgtaata	4500
tatgctgtct	atttctaatt	ttcacattca	tattttgagg	ttctatctta	ttttaataga	4560
gaacagactt	ctcaaaaaat	cttcagaagc	agcttattat	tgaaatatcg	aaatattgaa	4620
ataaaccggg	tggggttaga	ttactcatct	gtccaccaag	tgggacattt	gcatggactg	4680
ggggcttaaa	ggacttagaa	gagacctgta	agtaaatacct	gaaaatgagc	caatccccac	4740
ttgaatgggt	actggagtaa	accacacctt	accaccccaa	ttacagcacc	cgaggccgat	4800
aaaccaactt	ggctctgggt	catttttctt	ttcttcattt	gtgatgctca	gattcaaaat	4860
gtgtgttcta	cactgttaca	ggcttctctt	ttgtttgatt	aaagatttta	gtcctacttt	4920
tgtatggaca	cattagaata	ttcagagacc	aaaatagaag	aatttgctgt	tagatatatt	4980
tcagaagtca	gcagatttgt	ggcaaatcat	ttatttgcct	ttttaaaaaat	tcatttaagc	5040
agttcagaga	gtagactact	cagaaaatta	tttcacgtaa	ttgtctaaga	ggtcaatatt	5100
ttttaatgca	tattgaatca	aataaagtgc	tctaaagaaa	ttattataca	aattcctttg	5160
ggttgttttt	cttttcttaa	caaggggttg	gggtaaacag	gaatatgatt	caggcctttct	5220
ggttgtgtat	ttaaagagta	ttgattttat	tattactatt	gatttacttt	attcctggct	5280
tccttttcac	ttttctttca	atttttaaaa	aataatttaa	gccgttgaaa	atataccaaa	5340
ctgttgaaac	attttactca	aattttaaat	tcctaaaaat	gttttttaat	aagagggaga	5400
aaattattta	aaaataactta	tgccatgccc	aatttccttc	ttttttcaca	aaatccatga	5460
tttcagtttg	taagtagaca	tatatctaag	ggcacatttt	tggaagtga	ggaatagcag	5520
cagtataact	tcattttgtc	aggcctttga	gttctaatat	tttgtattgc	tcttcaaatg	5580
gatcctttta	aaaaaattgt	agataatgag	tcataaatag	attctgccaa	ctgaggggag	5640
aaacatttta	agtaaataatt	tttcagtatt	tggggcctta	aaaaataatt	gtgtttcctt	5700
aaaattacat	gttagataga	gttttttaggt	ttttttgggt	ttaagattgg	ttaaagcaat	5760
ttaaaagcca	cttttttgtc	aacattttaat	agcctccact	tctgttaaga	taatgtatac	5820
tgctgaggaa	ttactattaa	tagctatcaa	cataccacca	ttaaattaag	gtattcactt	5880
tagatttttt	attaaagctt	ttttcttgca	cactgatcgt	tgtgtttcta	agctgatttt	5940
ttcagctcta	atatacctat	ggttaaaaag	tataaaaact	taaattgata	tttagatata	6000
tgttttccta	ttagtttatg	ttttaaaaag	acaaaattgt	atctgtcagt	ccctgaaggc	6060
agtttgtttt	tatactctct	cacatttgta	tttgtttttt	aaatggcagt	attttagaag	6120
atttgagaaa	aagtcacat	aataatgttt	tcttaaaagc	ttttaagttt	tttgctgtac	6180
ttcaatttac	ttcttccatc	agaaaactaa	gaacaaagtg	ttgctcagtc	tgttccgctg	6240

JPOXMLDOC01-seq1

acctaaat	gtgttttcag	cacttggctc	agccaattca	ctgagtgaag	gaattgcttt	6300
atgaggcaaa	gcatgtgaaa	gttctaaagt	atggttagat	tgtaggtcgt	gctctatatg	6360
gaaacatcaa	accattacta	cagagaaatg	ataaggcatt	ggatccacta	ttgaaattat	6420
tatTTTTgga	tcaacaagtt	ggTactttct	gacttctgta	tcttaacata	agggaaat	6480
aggtaatgct	aagtcagttg	tctcattttt	tgtgataagt	tttggaat	ttagttaatt	6540
gaaataaata	atgcttttaa	atagaagtaa	aagggttata	agtgtgcaaa	ttgtagattt	6600
atcaattacc	tcagcaggta	tcctgccatg	taattattag	tgattagtgt	taataagata	6660
atagattcag	gtcttccaac	tatgcccttg	gattgtggcc	tactgtatgt	tattaaatgg	6720
tctcttacta	tccaaaatgg	gagtagatgc	tgtggccccg	tctcccttgg	cttttacgtc	6780
ccatatccac	ccccattcat	gtacaacatg	tgaaatataa	aaatctcatt	tcttgtcaaa	6840
atcagcactg	cttatttgca	tactcagcat	cggatcagtg	agtagtttta	taaaaaatcc	6900
acgcacccaa	ctcccttagt	taaaacagat	tcttaattca	taccatgaat	tcttaatttc	6960
tgtaccatct	atgttaatga	tctgctgaag	gtgactcaag	atTTTcaagg	tgtaatacag	7020
tttgatcatg	taccggacct	ggatatttaa	TTTTTTTcc	ctcacagtta	atctcctcct	7080
tgataaagca	ataacactgc	tttgagtctg	ttgcctaata	gcatgtcaga	atcctctcct	7140
ggatggtgat	tttataggaa	agtttgatg	catatcacc	agtctatctt	ttaaaaatta	7200
agaaatttaa	atgtatgctg	gaagtaatga	cactatattg	tggcatttta	ttttaaaaat	7260
tggggaaagt	tgcatat	tttaaaagta	agtgtttgag	taaaaaaatt	gaagggtactt	7320
ttttaaggaa	aaaaatttat	atgccacagt	ttacatagac	atttcagatt	caacacgtac	7380
tcttgaatat	aatgggttct	tttacttgg	caaaatgcat	gtatagcatt	tctttcatct	7440
tagttccttg	tgtttgccta	tgtggtcctt	tatatat	ttattgtatc	gaagaaacaa	7500
aactatcttc	aaaaataagt	taatttggat	atatttgtca	tatcaaaacta	caaagtgtac	7560
aaagttaagt	ttagcccttt	tctagaaagt	gatctttaa	attaaaaatg	ctcctctttt	7620
aaattcacca	aatttatgtg	tgggaaggca	ccaaaatgat	tttgtaagt	ccactgcaat	7680
attccctttc	aagtgtggcc	taaatttcaa	tcttaaggat	ggaatgcatg	tctgctcctt	7740
gttctgaaaa	atgtaggc	ctactacatt	ttaaaacaca	gtgaaacata	tacataagcc	7800
tataaaaaaa	gatttgtgca	atttgaaagc	ctgttaat	tttatgtaga	catacctaca	7860
cacgaaaggg	ttaaattcac	agccttacta	gttccttgct	tccagtattt	caattggtct	7920
cctccccctca	ttattattat	tactactagt	actattat	ttgcacatag	ttactgccc	7980
ttcaatatga	ttcttaaaaa	gtgctgtttc	tgtggtatcg	tattctctaa	ataatcatat	8040
ttaatttttt	aaaacaaggt	tgcagtttct	aattgtttcg	ttcctgtgtt	tttgctggtg	8100
tgtaataaaa	gcaagttttt	tcttttcatg	gttattta	acattagctg	cctgtaaata	8160
attcttggtta	taatgctctg	gaatgtgttg	tagaagttgt	attagattag	ttttaaaccc	8220
ttgtttgaaa	gccacattgt	tttggttatt	tctattaaat	tagaaaattg	aaaaagtttt	8280

caaatgaa

<210> 45
 <211> 1127
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> TRIM33 isoform alpha (NP_056990.3)

<400> 45

Met Ala Glu Asn Lys Gly Gly Gly Glu Ala Glu Ser Gly Gly Gly Gly
 1 5 10 15

Ser Gly Ser Ala Pro Val Thr Ala Gly Ala Ala Gly Pro Ala Ala Gln
 20 25 30

Glu Ala Glu Pro Pro Leu Thr Ala Val Leu Val Glu Glu Glu Glu
 35 40 45

Glu Gly Gly Arg Ala Gly Ala Glu Gly Gly Ala Ala Gly Pro Asp Asp
 50 55 60

Gly Gly Val Ala Ala Ala Ser Ser Gly Ser Ala Gln Ala Ala Ser Ser
 65 70 75 80

Pro Ala Ala Ser Val Gly Thr Gly Val Ala Gly Gly Ala Val Ser Thr
 85 90 95

Pro Ala Pro Ala Pro Ala Ser Ala Pro Ala Pro Gly Pro Ser Ala Gly
 100 105 110

Pro Pro Pro Gly Pro Pro Ala Ser Leu Leu Asp Thr Cys Ala Val Cys
 115 120 125

Gln Gln Ser Leu Gln Ser Arg Arg Glu Ala Glu Pro Lys Leu Leu Pro
 130 135 140

Cys Leu His Ser Phe Cys Leu Arg Cys Leu Pro Glu Pro Glu Arg Gln
 145 150 155 160

Leu Ser Val Pro Ile Pro Gly Gly Ser Asn Gly Asp Ile Gln Gln Val
 165 170 175

Gly Val Ile Arg Cys Pro Val Cys Arg Gln Glu Cys Arg Gln Ile Asp
 180 185 190

Leu Val Asp Asn Tyr Phe Val Lys Asp Thr Ser Glu Ala Pro Ser Ser
 195 200 205

Ser Asp Glu Lys Ser Glu Gln Val Cys Thr Ser Cys Glu Asp Asn Ala
 Page 125

JPOXMLDOC01-seq1

210

215

220

Ser₂₂₅ Ala Val Gly Phe₂₃₀ Cys₂₃₀ Val Glu Cys Gly₂₃₅ Glu₂₃₅ Trp Leu Cys Lys Thr₂₄₀

Cys Ile Glu Ala His₂₄₅ Gln Arg Val Lys₂₅₀ Phe₂₅₀ Thr Lys Asp His₂₅₅ Leu₂₅₅ Ile

Arg Lys Lys Glu₂₆₀ Asp Val Ser Glu₂₆₅ Ser₂₆₅ Val Gly Ala Ser Gly₂₇₀ Gln Arg

Pro Val Phe₂₇₅ Cys Pro Val His₂₈₀ Lys₂₈₀ Gln Glu Gln Leu₂₈₅ Lys₂₈₅ Leu Phe Cys

Glu₂₉₀ Thr₂₉₀ Cys Asp Arg Leu₂₉₅ Thr₂₉₅ Cys Arg Asp Cys₃₀₀ Gln₃₀₀ Leu Leu Glu His

Lys₃₀₅ Glu His Arg Tyr Gln₃₁₀ Phe Leu Glu Glu₃₁₅ Ala₃₁₅ Phe Gln Asn Gln₃₂₀ Lys₃₂₀

Gly Ala Ile Glu Asn₃₂₅ Leu Leu Ala Lys₃₃₀ Leu₃₃₀ Leu Glu Lys Lys₃₃₅ Asn₃₃₅ Tyr

Val His Phe₃₄₀ Ala₃₄₀ Ala Thr Gln Val₃₄₅ Gln₃₄₅ Asn Arg Ile Lys₃₅₀ Glu₃₅₀ Val Asn

Glu Thr Asn₃₅₅ Lys Arg Val Glu₃₆₀ Gln₃₆₀ Glu Ile Lys Val₃₆₅ Ala₃₆₅ Ile Phe Thr

Leu Ile₃₇₀ Asn Glu Ile Asn₃₇₅ Lys₃₇₅ Lys Gly Lys Ser₃₈₀ Leu₃₈₀ Leu Gln Gln₃₈₅ Leu

Glu₃₈₅ Asn Val Thr Lys₃₉₀ Glu₃₉₀ Arg Gln Met Lys₃₉₅ Leu₃₉₅ Leu Gln Gln₄₀₀ Gln₄₀₀ Asn

Asp Ile Thr Gly₄₀₅ Leu₄₀₅ Ser Arg Gln Val₄₁₀ Lys₄₁₀ His Val Met Asn₄₁₅ Phe₄₁₅ Thr

Asn Trp Ala Ile₄₂₀ Ala Ser Gly Ser₄₂₅ Ser₄₂₅ Thr Ala Leu Leu₄₃₀ Tyr₄₃₀ Ser Lys

Arg Leu Ile₄₃₅ Thr Phe Gln Leu Arg₄₄₀ His Ile Leu Lys₄₄₅ Ala₄₄₅ Arg Cys Asp

Pro Val Pro Ala Ala Asn₄₅₀ Gly₄₅₅ Ala Ile Arg Phe₄₆₀ His₄₆₀ Cys Asp Pro Thr

Phe₄₆₅ Trp Ala Lys Asn₄₇₀ Val₄₇₀ Val Asn Leu Gly₄₇₅ Asn₄₇₅ Leu Val Ile Glu₄₈₀ Ser₄₈₀

Lys Pro Ala Pro Gly Tyr Thr Pro Asn Val Val Val Gly Gln Val Pro

JPOXMLDOC01-seq1

485

490

495

Pro Gly Thr Asn His Ile Ser Lys Thr Pro Gly Gln Ile Asn Leu Ala
500 505 510

Gln Leu Arg Leu Gln His Met Gln Gln Gln Val Tyr Ala Gln Lys His
515 520 525

Gln Gln Leu Gln Gln Met Arg Met Gln Gln Pro Pro Ala Pro Val Pro
530 535 540

Thr Thr Thr Thr Thr Thr Gln Gln His Pro Arg Gln Ala Ala Pro Gln
545 550 555 560

Met Leu Gln Gln Gln Pro Pro Arg Leu Ile Ser Val Gln Thr Met Gln
565 570 575

Arg Gly Asn Met Asn Cys Gly Ala Phe Gln Ala His Gln Met Arg Leu
580 585 590

Ala Gln Asn Ala Ala Arg Ile Pro Gly Ile Pro Arg His Ser Gly Pro
595 600 605

Gln Tyr Ser Met Met Gln Pro His Leu Gln Arg Gln His Ser Asn Pro
610 615 620

Gly His Ala Gly Pro Phe Pro Val Val Ser Val His Asn Thr Thr Ile
625 630 635 640

Asn Pro Thr Ser Pro Thr Thr Ala Thr Met Ala Asn Ala Asn Arg Gly
645 650 655

Pro Thr Ser Pro Ser Val Thr Ala Ile Glu Leu Ile Pro Ser Val Thr
660 665 670

Asn Pro Glu Asn Leu Pro Ser Leu Pro Asp Ile Pro Pro Ile Gln Leu
675 680 685

Glu Asp Ala Gly Ser Ser Ser Leu Asp Asn Leu Leu Ser Arg Tyr Ile
690 695 700

Ser Gly Ser His Leu Pro Pro Gln Pro Thr Ser Thr Met Asn Pro Ser
705 710 715 720

Pro Gly Pro Ser Ala Leu Ser Pro Gly Ser Ser Gly Leu Ser Asn Ser
725 730 735

His Thr Pro Val Arg Pro Pro Ser Thr Ser Ser Thr Gly Ser Arg Gly
740 745 750

Ser Cys Gly Ser Ser Gly Arg Thr Ala Glu Lys Thr Ser Leu Ser Phe
Page 127

JPOXMLDOC01-seq1

755

760

765

Lys Ser Asp Gln Val Lys Val Lys Gln Glu Pro Gly Thr Glu Asp Glu
 770 775 780

Ile Cys Ser Phe Ser Gly Gly Val Lys Gln Glu Lys Thr Glu Asp Gly
 785 790 795 800

Arg Arg Ser Ala Cys Met Leu Ser Ser Pro Glu Ser Ser Leu Thr Pro
 805 810 815

Pro Leu Ser Thr Asn Leu His Leu Glu Ser Glu Leu Asp Ala Leu Ala
 820 825 830

Ser Leu Glu Asn His Val Lys Ile Glu Pro Ala Asp Met Asn Glu Ser
 835 840 845

Cys Lys Gln Ser Gly Leu Ser Ser Leu Val Asn Gly Lys Ser Pro Ile
 850 855 860

Arg Ser Leu Met His Arg Ser Ala Arg Ile Gly Gly Asp Gly Asn Asn
 865 870 875 880

Lys Asp Asp Asp Pro Asn Glu Asp Trp Cys Ala Val Cys Gln Asn Gly
 885 890 895

Gly Asp Leu Leu Cys Cys Glu Lys Cys Pro Lys Val Phe His Leu Thr
 900 905 910

Cys His Val Pro Thr Leu Leu Ser Phe Pro Ser Gly Asp Trp Ile Cys
 915 920 925

Thr Phe Cys Arg Asp Ile Gly Lys Pro Glu Val Glu Tyr Asp Cys Asp
 930 935 940

Asn Leu Gln His Ser Lys Lys Gly Lys Thr Ala Gln Gly Leu Ser Pro
 945 950 955 960

Val Asp Gln Arg Lys Cys Glu Arg Leu Leu Leu Tyr Leu Tyr Cys His
 965 970 975

Glu Leu Ser Ile Glu Phe Gln Glu Pro Val Pro Ala Ser Ile Pro Asn
 980 985 990

Tyr Tyr Lys Ile Ile Lys Lys Pro Met Asp Leu Ser Thr Val Lys Lys
 995 1000 1005

Lys Leu Gln Lys Lys His Ser Gln His Tyr Gln Ile Pro Asp Asp
 1010 1015 1020

Phe Val Ala Asp Val Arg Leu Ile Phe Lys Asn Cys Glu Arg Phe
 Page 128

JPOXMLDOC01-seq1

1025

1030

1035

Asn Glu Met Met Lys Val Val Gln Val Tyr Ala Asp Thr Gln Glu
1040 1045 1050

Ile Asn Leu Lys Ala Asp Ser Glu Val Ala Gln Ala Gly Lys Ala
1055 1060 1065

Val Ala Leu Tyr Phe Glu Asp Lys Leu Thr Glu Ile Tyr Ser Asp
1070 1075 1080

Arg Thr Phe Ala Pro Leu Pro Glu Phe Glu Gln Glu Glu Asp Asp
1085 1090 1095

Gly Glu Val Thr Glu Asp Ser Asp Glu Asp Phe Ile Gln Pro Arg
1100 1105 1110

Arg Lys Arg Leu Lys Ser Asp Glu Arg Pro Val His Ile Lys
1115 1120 1125

<210> 46
<211> 1110
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> TRIM33 isoform beta (NP_148980.2)

<400> 46

Met Ala Glu Asn Lys Gly Gly Gly Glu Ala Glu Ser Gly Gly Gly Gly
1 5 10 15

Ser Gly Ser Ala Pro Val Thr Ala Gly Ala Ala Gly Pro Ala Ala Gln
20 25 30

Glu Ala Glu Pro Pro Leu Thr Ala Val Leu Val Glu Glu Glu Glu
35 40 45

Glu Gly Gly Arg Ala Gly Ala Glu Gly Gly Ala Ala Gly Pro Asp Asp
50 55 60

Gly Gly Val Ala Ala Ala Ser Ser Gly Ser Ala Gln Ala Ala Ser Ser
65 70 75 80

Pro Ala Ala Ser Val Gly Thr Gly Val Ala Gly Gly Ala Val Ser Thr
85 90 95

Pro Ala Pro Ala Pro Ala Ser Ala Pro Ala Pro Gly Pro Ser Ala Gly
100 105 110

Pro Pro Pro Gly Pro Pro Ala Ser Leu Leu Asp Thr Cys Ala Val Cys

115

120

125

Gln Gln Ser Leu Gln Ser Arg Arg Glu Ala Glu Pro Lys Leu Leu Pro
 130 135 140

Cys Leu His Ser Phe Cys Leu Arg Cys Leu Pro Glu Pro Glu Arg Gln
 145 150 155 160

Leu Ser Val Pro Ile Pro Gly Gly Ser Asn Gly Asp Ile Gln Gln Val
 165 170 175

Gly Val Ile Arg Cys Pro Val Cys Arg Gln Glu Cys Arg Gln Ile Asp
 180 185 190

Leu Val Asp Asn Tyr Phe Val Lys Asp Thr Ser Glu Ala Pro Ser Ser
 195 200 205

Ser Asp Glu Lys Ser Glu Gln Val Cys Thr Ser Cys Glu Asp Asn Ala
 210 215 220

Ser Ala Val Gly Phe Cys Val Glu Cys Gly Glu Trp Leu Cys Lys Thr
 225 230 235 240

Cys Ile Glu Ala His Gln Arg Val Lys Phe Thr Lys Asp His Leu Ile
 245 250 255

Arg Lys Lys Glu Asp Val Ser Glu Ser Val Gly Ala Ser Gly Gln Arg
 260 265 270

Pro Val Phe Cys Pro Val His Lys Gln Glu Gln Leu Lys Leu Phe Cys
 275 280 285

Glu Thr Cys Asp Arg Leu Thr Cys Arg Asp Cys Gln Leu Leu Glu His
 290 295 300

Lys Glu His Arg Tyr Gln Phe Leu Glu Glu Ala Phe Gln Asn Gln Lys
 305 310 315 320

Gly Ala Ile Glu Asn Leu Leu Ala Lys Leu Leu Glu Lys Lys Asn Tyr
 325 330 335

Val His Phe Ala Ala Thr Gln Val Gln Asn Arg Ile Lys Glu Val Asn
 340 345 350

Glu Thr Asn Lys Arg Val Glu Gln Glu Ile Lys Val Ala Ile Phe Thr
 355 360 365

Leu Ile Asn Glu Ile Asn Lys Lys Gly Lys Ser Leu Leu Gln Gln Leu
 370 375 380

Glu Asn Val Thr Lys Glu Arg Gln Met Lys Leu Leu Gln Gln Gln Asn
 Page 130

JPOXMLDOC01-seq1

385 390 395 400
 Asp Ile Thr Gly Leu Ser Arg Gln Val Lys His Val Met Asn Phe Thr
 405 410 415
 Asn Trp Ala Ile Ala Ser Gly Ser Ser Thr Ala Leu Leu Tyr Ser Lys
 420 425 430
 Arg Leu Ile Thr Phe Gln Leu Arg His Ile Leu Lys Ala Arg Cys Asp
 435 440 445
 Pro Val Pro Ala Ala Asn Gly Ala Ile Arg Phe His Cys Asp Pro Thr
 450 455 460
 Phe Trp Ala Lys Asn Val Val Asn Leu Gly Asn Leu Val Ile Glu Ser
 465 470 475 480
 Lys Pro Ala Pro Gly Tyr Thr Pro Asn Val Val Val Gly Gln Val Pro
 485 490 495
 Pro Gly Thr Asn His Ile Ser Lys Thr Pro Gly Gln Ile Asn Leu Ala
 500 505 510
 Gln Leu Arg Leu Gln His Met Gln Gln Gln Val Tyr Ala Gln Lys His
 515 520 525
 Gln Gln Leu Gln Gln Met Arg Met Gln Gln Pro Pro Ala Pro Val Pro
 530 535 540
 Thr Thr Thr Thr Thr Thr Gln Gln His Pro Arg Gln Ala Ala Pro Gln
 545 550 555 560
 Met Leu Gln Gln Gln Pro Pro Arg Leu Ile Ser Val Gln Thr Met Gln
 565 570 575
 Arg Gly Asn Met Asn Cys Gly Ala Phe Gln Ala His Gln Met Arg Leu
 580 585 590
 Ala Gln Asn Ala Ala Arg Ile Pro Gly Ile Pro Arg His Ser Gly Pro
 595 600 605
 Gln Tyr Ser Met Met Gln Pro His Leu Gln Arg Gln His Ser Asn Pro
 610 615 620
 Gly His Ala Gly Pro Phe Pro Val Val Ser Val His Asn Thr Thr Ile
 625 630 635 640
 Asn Pro Thr Ser Pro Thr Thr Ala Thr Met Ala Asn Ala Asn Arg Gly
 645 650 655
 Pro Thr Ser Pro Ser Val Thr Ala Ile Glu Leu Ile Pro Ser Val Thr
 660 665 670

JPOXMLDOC01-seq1

660

665

670

Asn Pro Glu Asn Leu Pro Ser Leu Pro Asp Ile Pro Pro Ile Gln Leu
 675 680 685
 Glu Asp Ala Gly Ser Ser Ser Leu Asp Asn Leu Leu Ser Arg Tyr Ile
 690 695 700
 Ser Gly Ser His Leu Pro Pro Gln Pro Thr Ser Thr Met Asn Pro Ser
 705 710 715 720
 Pro Gly Pro Ser Ala Leu Ser Pro Gly Ser Ser Gly Leu Ser Asn Ser
 725 730 735
 His Thr Pro Val Arg Pro Pro Ser Thr Ser Ser Thr Gly Ser Arg Gly
 740 745 750
 Ser Cys Gly Ser Ser Gly Arg Thr Ala Glu Lys Thr Ser Leu Ser Phe
 755 760 765
 Lys Ser Asp Gln Val Lys Val Lys Gln Glu Pro Gly Thr Glu Asp Glu
 770 775 780
 Ile Cys Ser Phe Ser Gly Gly Val Lys Gln Glu Lys Thr Glu Asp Gly
 785 790 795 800
 Arg Arg Ser Ala Cys Met Leu Ser Ser Pro Glu Ser Ser Leu Thr Pro
 805 810 815
 Pro Leu Ser Thr Asn Leu His Leu Glu Ser Glu Leu Asp Ala Leu Ala
 820 825 830
 Ser Leu Glu Asn His Val Lys Ile Glu Pro Ala Asp Met Asn Glu Ser
 835 840 845
 Cys Lys Gln Ser Gly Leu Ser Ser Leu Val Asn Gly Lys Ser Pro Ile
 850 855 860
 Arg Ser Leu Met His Arg Ser Ala Arg Ile Gly Gly Asp Gly Asn Asn
 865 870 875 880
 Lys Asp Asp Asp Pro Asn Glu Asp Trp Cys Ala Val Cys Gln Asn Gly
 885 890 895
 Gly Asp Leu Leu Cys Cys Glu Lys Cys Pro Lys Val Phe His Leu Thr
 900 905 910
 Cys His Val Pro Thr Leu Leu Ser Phe Pro Ser Gly Asp Trp Ile Cys
 915 920 925
 Thr Phe Cys Arg Asp Ile Gly Lys Pro Glu Val Glu Tyr Asp Cys Asp

JPOXMLDOC01-seq1

930

935

940

Asn Leu Gln His Ser Lys Lys Gly Lys Thr Ala Gln Gly Leu Ser Pro
945 950 955 960

Val Asp Gln Arg Lys Cys Glu Arg Leu Leu Leu Tyr Leu Tyr Cys His
965 970 975

Glu Leu Ser Ile Glu Phe Gln Glu Pro Val Pro Ala Ser Ile Pro Asn
980 985 990

Tyr Tyr Lys Ile Ile Lys Lys Pro Met Asp Leu Ser Thr Val Lys Lys
995 1000 1005

Lys Leu Gln Lys Lys His Ser Gln His Tyr Gln Ile Pro Asp Asp
1010 1015 1020

Phe Val Ala Asp Val Arg Leu Ile Phe Lys Asn Cys Glu Arg Phe
1025 1030 1035

Asn Glu Ala Asp Ser Glu Val Ala Gln Ala Gly Lys Ala Val Ala
1040 1045 1050

Leu Tyr Phe Glu Asp Lys Leu Thr Glu Ile Tyr Ser Asp Arg Thr
1055 1060 1065

Phe Ala Pro Leu Pro Glu Phe Glu Gln Glu Glu Asp Asp Gly Glu
1070 1075 1080

Val Thr Glu Asp Ser Asp Glu Asp Phe Ile Gln Pro Arg Arg Lys
1085 1090 1095

Arg Leu Lys Ser Asp Glu Arg Pro Val His Ile Lys
1100 1105 1110