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# DESCRIPTION

## Technical Field

**[0001]** The present invention relates to a method for detecting a cancer with CAPRIN-1 as a tumor marker.

## Background Art

**[0002]** Cancer is the leading cause of death. This disease is currently treated principally by surgical therapy in combination with radiation therapy and/or chemotherapy. Owing to previous advances in medical technology, cancer is now a disease highly curable if early detected, depending on its type. Therefore, there is a demand for a method for detecting a cancer which places neither physical nor economic burdens on cancer patients and can be achieved by convenient tests.

**[0003]** Recently, methods for assaying tumor products such as tumor markers have been widely available. The tumor products refer to, for example, tumor-related antigens, enzymes, particular proteins, metabolites, oncogenes, oncogene products, and tumor suppressor genes. Carcinoembryonic antigen CEA, glycoprotein CA19-9, prostate-specific antigen PSA, calcitonin (peptide hormone produced in the thyroid gland), and the like are exploited as tumor markers in cancer diagnosis for some cancers. For many types of cancers, however, tumor markers useful in cancer diagnosis have not yet been found. In addition, a large majority of currently known tumor markers is present only in very small amounts (of the order of pg/mL) in body fluids and requires highly sensitive assay methods or special techniques for detecting these markers. Under such circumstances, it can be expected that doors will be opened for diagnostic use for various types of cancers if a novel cancer testing approach capable of highly sensitively detecting various types of cancers by convenient operation can be provided.

**[0004]** Meanwhile, in spite of recent development of novel surgical techniques or discovery of novel anticancer agents, the existing cancer treatment has an insufficiently improved outcome. This is because an effective cancer diagnosis technique has not been established for many cancers, except for some cancers. Inability to detect these cancers early is partly responsible for this situation.

**[0005]** With recent advances in molecular biology or cancer immunology, antibodies specifically reacting with cancer, molecular targeting drugs for cancer antigens related to malignant transformation or cancer exacerbation, and the like have been identified, raising expectations on specific cancer therapy targeting cancer antigens.

**[0006]** Among others, a plurality of antibody drugs for cancer treatment targeting antigenic proteins on cancer cells have been launched and used in the cancer treatment. These antibody drugs have received attention because of their certain efficacy as cancer-specific therapeutic agents. A large majority of antigenic proteins targeted by the drugs, however, are also expressed in normal cells. As a result of administering the antibodies, cancer cells as well as normal cells expressing the antigens are therefore damaged, resulting in undesired adverse reactions. In addition, the effects of cancer treatment differ very largely among individuals due to various factors of the individual cancer patients. For example, surgery, chemotherapy, or radiation therapy largely varies in the treatment and prognosis depending on the stages of cancers. Different persons are known to have distinctive sensitivities to the same therapeutic drug for cancers. This indicates that a certain drug is effective for some patients but ineffective for others due to the diversity of individuals.

**[0007]** Thus, as for some therapeutic drugs, their administration to cancer patients is determined by measuring in advance the expression of disease-related genes or proteins in the patients and evaluating whether a particular drug is effective for a patient expressing a particular gene or protein. Specifically, the presence of a cancer antigen in a sample, for example, serum or tissue, derived from a cancer patient is tested in clinical practice by use of a detection method for assaying a disease-related gene or protein of a certain kind of cancer. Then, the administration of a cancer antigen-specific therapeutic drug is determined. For example, cancer tissues from a large bowel cancer patient are evaluated by an immunohistochemical staining EGFR detection method "EGFR pharm (Dako)" to predict the effectiveness of Erbitux(R) (cetuximab) for the large bowel cancer. Then, the administration of Erbitux is determined. Further, cancer tissues from a breast cancer patient are evaluated by an immunohistochemical staining Her2 detection method "HercepTest" to predict the effectiveness of Herceptin(R) (trastuzumab) for the breast cancer. Then, the application of Herceptin is determined.

**[0008]** Incidentally, companion animals have been raised recently as family members and often have lifestyles similar to those of their owners. For this reason, from the occurrence of cancers in companion animals, it can reportedly be predicted that their owners have the high risk of developing cancers in the future.

**[0009]** Dogs, typical companion animals, are known to age 7 times more quickly than humans. Reportedly, the number of dogs currently raised is approximately 6.7 million in Japan and approximately 17.64 million in the USA. Rabies shots as well as combined vaccines such as quintuple, septuple, or octuple combination shots are generally available, leading to decreased rates of highly lethal infections including canine parvovirus infection, canine distemper infection, canine parainfluenza virus infection (kennel cough), canine adenovirus type 2 infection (kennel cough), canine infectious hepatitis, canine coronavirus infection, and leptospirosis. An average dog life-span has therefore been increased, and 7-year-old or older dogs account for 35.5% of the total number of pet dogs. The causes of death such as cancer, hypertension, and heart disease are ever increasing in dogs, as in humans. In the USA, approximately 4 million dogs are yearly diagnosed with cancers. Also in Japan, approximately 1.6 million dogs allegedly have some potential tumor. Checkup examination, however, is not very common in companion animals, unlike humans. This leads to the late detection of disease. In most cases, their owners notice pets' symptoms for the first time after tumors have already become large, and then visit animal hospitals. If such large tumors are malignant, even surgical therapy (e.g., surgical operation) or medication using anticancer agents or the like is very often too late to cure the tumors. Tumors confirmed by veterinarians to be malignant are generally treated with anticancer agents without surgery. Even in the case of performing surgery, it is required to secure surgical margins or to take stringent measures for surgery such as measures against the spread of blood or cells during surgery. Desirably, treatment with anticancer agents is initiated immediately after surgery, and a follow-up is also performed at short intervals. Thus, the medication using therapeutic drugs for cancers is also essential for the cancer-affected companion animals. A detection method, if any, for assaying a disease-related gene or protein of a certain kind of cancer permits more effective treatment than ever and is advantageous both for owners and for veterinarians.

**[0010]** Cytoplasmic- and proliferation-associated protein 1 (CAPRIN-1) is an intracellular protein known to be expressed upon activation or cell division of resting normal cells and to form cytoplasmic stress granules with intracellular RNAs to participate in the regulation of transport and translation of mRNAs. Meanwhile, it has been found that: CAPRIN-1 is highly expressed on the membrane surface of breast cancer cells; and an antibody against CAPRIN-1 exerts strong antitumor effects on breast cancer cells (Patent Literature 1). According to another report, the expression of CAPRIN-1 in a patient-derived sample can be measured using an antibody binding to CAPRIN-1 expressed on cell surface to thereby detect a cancer and to evaluate the grade of the cancer (Patent Literature 2). Specifically, the report states that a plasma membrane protein CAPRIN-1 may serve as a target for cancer treatment or the like. As mentioned above, due to the diversity of cancer patients, it is required to test the presence of CAPRIN-1 in a cancer patient-derived sample for determining the administration of a CAPRIN-1-targeting therapeutic drug, for example, an antibody. Nonetheless, there exists no report on a method for detecting CAPRIN-1 for the application of such a specific therapeutic drug, or there exists no reagent for detecting a cancer using a cancer patient-derived sample.

**[0011]** Patent Literature 3, which is prior art under Art 54(3) EPC, discloses an antibody with heavy and light chain variable region sequences of SEQ ID NOs:70 and 71 of the present application.

**Citation List**

**Patent Literature**

**[0012]**

Patent Literature 1: WO2010/016526

Patent Literature 2: WO2010/016527

Patent Literature 3: EP2740794

## Summary of Invention

### Technical Problem

**[0013]** An object of the present invention is to provide a cancer detection approach useful in the diagnosis of a cancer. Another object of the present invention is to provide a method for detecting a cancer which involves determining the presence and the amount of CAPRIN-1 in a sample of a cancer patient in order to determine the administration of a CAPRIN-1-targeting drug to the cancer patient, and a drug and a kit for the diagnosis of a cancer.

### Solution to Problem

**[0014]** As a result of conducting diligent studies, the present inventors have obtained cDNAs encoding proteins binding to antibodies present in cancer-bearing organism-derived serum by SEREX using a dog testis-derived cDNA library and the serum of cancer-bearing dogs, and prepared dog CAPRIN-1s having the amino acid sequences shown in SEQ ID NOs: 6, 8, 10, 12, and 14 on the basis of the cDNAs. The present inventors have also prepared human CAPRIN-1s having the amino acid sequences shown in SEQ ID NOs: 2 and 4 on the basis of human homologous genes of the obtained genes. Consequently, the present inventors have found that: genes encoding these proteins are specifically expressed in dog and human testis, respectively, and in malignant cancer cells (see Example 1 mentioned later); and monoclonal antibodies prepared using, as antigens, recombinant polypeptides prepared on the basis of the amino acid sequences of these proteins can bind to CAPRIN-1 in various cancer tissues and damage cancer cells having CAPRIN-1 on their surface. As a result, the present inventors have gained the finding that CAPRIN-1 can be used as a target for cancer treatment. The present inventors have further found that CAPRIN-1 can be specifically detected from cancer patient-derived samples by use of the monoclonal antibodies mentioned above. Specifically, the present invention provides a method for detecting a cancer, comprising measuring the expression of CAPRIN-1 using a predetermined anti-CAPRIN-1 antibody for application to a sample separated from an organism. In addition, the present invention has established a method for detecting CAPRIN-1 in a cancer patient-derived sample and evaluating the expression level thereof by an immunological assay method using any of the monoclonal antibodies mentioned above, for example, by ELISA for cancer patient-derived serum using a predetermined anti-CAPRIN-1 monoclonal antibody or an immunohistochemical staining method for cancer tissues. The present inventors have also found that as a result of evaluating a cancer-derived sample by this method, the applicability of a CAPRIN-1-targeting drug to a patient is indicated if the expression of CAPRIN-1 and a high abundance thereof are found in the patient. On the basis of these findings, the present invention has been completed.

**[0015]** The present invention provides a method as defined in the claims for detecting a cancer which is applied to a sample separated from an organism, the method comprising detecting CAPRIN-1 in the sample and measuring the amount thereof. The present invention also provides a diagnosis method as defined in the claims comprising measuring the expression level of CAPRIN-1 in a tissue before administration of a CAPRIN-1-targeting drug to a patient to thereby predict the effectiveness thereof and reveal the applicability of a therapeutic drug against CAPRIN-1 (e.g., whether a CAPRIN-1-targeting drug, for example, an antibody, can be applied to the cancer patient). The present invention further provides an antibody or antigen-binding fragment thereof, for use in the diagnosis of a cancer by administration to the body, and related uses of such antibodies or fragments, also as defined in the claims.

## Advantageous Effects of Invention

**[0016]** The present invention provides a novel method for detecting a cancer, comprising measuring the expression of CAPRIN-1 in a sample separated from a cancer patient. As specifically shown in Examples mentioned later, antibodies prepared using, as antigens, recombinant polypeptides prepared on the basis of the amino acid sequence of CAPRIN-1 (also referred to as Caprin-1 or CAPRIN-1 protein) specifically react with CAPRIN-1 in the body fluids (e.g., serum) or tissues of cancer patients. As also described later in Examples, CAPRIN-1 itself is specifically expressed at high levels in various cancer tissues. The presence and the amount of CAPRIN-1 in a sample separated from a cancer patient can therefore be measured to thereby detect a cancer. In addition, the presence or absence of sensitivity to a CAPRIN-1-targeting drug such as a CAPRIN-1-targeting therapeutic drug, for example, an antibody drug, can be determined in advance to thereby select a patient to which this drug is applicable. Specifically, the expression and the amount of CAPRIN-1 can be measured in advance by the application of the present invention to a cancer patient to thereby provide more efficient treatment using an antibody against CAPRIN-1.

## Brief Description of Drawing

**[0017]** [Figure 1] Figure 1 is a diagram showing the expression patterns of a CAPRIN-1-encoding gene in normal tissues and tumor cell lines. Reference number 1 depicts the expression patterns of the gene encoding the CAPRIN-1 protein. Reference number 2 depicts the expression patterns of the GAPDH gene. The uppermost panel shows the results for dog normal tissues. The left middle panel shows the results for dog breast cancer tissues. The right middle panel shows the results for human breast cancer cell lines. The lowermost panel shows the results for various human cancer cell lines.

## Description of Embodiments

**[0018]** The method for detecting a cancer according to the present invention comprises measuring the amount (expression level) of CAPRIN-1 (CAPRIN-1 protein) in a sample separated from an organism (biological sample). The measurement of the expression level of CAPRIN-1 in a sample of a cancer patient can be carried out by use of, for example, an immunological assay method which involves detecting CAPRIN-1 using an antibody against CAPRIN-1 (anti-CAPRIN-1 antibody). Various immunological assay methods applicable to the measurement of the expression level of CAPRIN-1 are well known in the art. Examples thereof include immunohistochemical analysis, Western blot analysis, immunoprecipitation, molecular binding assay, ELISA, and biochemical enzyme activity assay. The results of measuring the expression level of CAPRIN-1 by such an assay method can also indicate, for example, the presence of CAPRIN-1 in the sample, the ratio of cells expressing CAPRIN-1, the distribution of expression sites in tissues, and expression intensity on a site basis. In this context, the "expression level" used herein includes the intracellular accumulation level and abundance of the protein.

**[0019]** The results of measuring the expression level of CAPRIN-1 in the sample can be classified into scores shown in Examples. A higher score indicates that CAPRIN-1 is contained in a larger amount in the biological sample (e.g., cancer tissue or cancer serum) of a cancer patient. In the present invention, the term "measurement" or "assay" encompasses all of detection and qualitative, quantitative, and semiquantitative approaches.

**[0020]** The amino acid sequence shown in SEQ ID NO: 6, 8, 10, 12, or 14 is the amino acid sequence of dog CAPRIN-1. The dog CAPRIN-1 having this amino acid sequence has been found by SEREX using a dog testis-derived cDNA library and serum derived from cancer-bearing dogs, and identified from the cDNA library as a polypeptide binding to an antibody specifically present in the serum derived from cancer-bearing dogs (see Example 1). CAPRIN-1 itself having the amino acid sequence of SEQ ID NO: 6, 8, 10, 12, or 14 can also be assayed as an antigen in dog tissues by the method mentioned above to thereby diagnose the presence or absence of sensitivity to a CAPRIN-1-targeting drug (see Examples).

**[0021]** In this context, the phrase "having an (the) amino acid sequence" used herein means that amino acid residues are arranged in the order presented in predetermined amino acid sequence information. Thus, for example, the "polypeptide having the amino acid sequence shown in SEQ ID NO: 2" means a polypeptide of 709 amino acid residues in size in which the amino acid residues are linked according to the amino acid sequence Met Pro Ser Ala ... (snip) ... Gln Gln Val Asn as shown in SEQ ID NO: 2. Also, for example, the "polypeptide having the amino acid sequence shown in SEQ ID NO: 2" is abbreviated to the "polypeptide of SEQ ID NO: 2". The same holds true for the phrase "having a (the) nucleotide sequence". The term "having" in the phrase "having an (the) amino acid sequence" and "having a (the) nucleotide sequence" may be replaced with the term "consisting of'.

**[0022]** The "polypeptide" used herein refers to a molecule that is formed through the peptide bonds of a plurality of amino acids, and encompasses not only a polypeptide molecule constituted by a large number of amino acids but a low-molecular-weight molecule having a small number of amino acids (oligopeptide or peptide) and a full-length protein. The polypeptide according to the present invention also encompasses the full-length proteins of CAPRIN-1 having the amino acid sequences shown in even-numbered SEQ ID NOs of SEQ ID NOs: 2 to 30.

**[0023]** In the method of the present invention, additional mammalian CAPRIN-1 other than the dog CAPRIN-1 of SEQ ID NO: 6, 8, 10, 12, or 14 can also be measured. In the present specification, such non-dog mammalian CAPRIN-1 is also referred to as a "homolog" of dog CAPRIN-1. The term "CAPRIN-1" encompasses CAPRIN-1 derived from not only dogs but other mammals. Examples of the additional mammalian CAPRIN-1 that may be measured in the method of the present invention include, but not limited to, human CAPRIN-1 and cat CAPRIN-1.

**[0024]** As specifically described below in Examples, mRNA encoding human CAPRIN-1 is significantly expressed at high levels in human testis and cancer cells, as with the dog CAPRIN-1 of SEQ ID NO: 6, 8, 10, 12, or 14. An anti-human CAPRIN-1 antibody, however, is not detected in the bodies of healthy humans. An anti-cat CAPRIN-1 antibody is not detected in the bodies of healthy cats, but is detected only in cancer-bearing cats. Thus, the applicability of a CAPRIN-1-targeting drug to a non-dog mammal can also be determined by the measurement of the expression level of CAPRIN-1 derived from the non-dog mammal.

**[0025]** The nucleotide sequence encoding human CAPRIN-1 and the amino acid sequence thereof are shown in SEQ ID NO: 1 or 3 and SEQ ID NO: 2 or 4, respectively, in the Sequence Listing. The sequence identity of human CAPRIN-1 to dog CAPRIN-1 is 94% for the nucleotide sequence and 98% for the amino acid sequence. Since the amino acid sequence identity of CAPRIN-1 is as very high as 98% even between dogs and humans, which are genetically distantly related mammals from each other, , many non-human and non-dog mammalian CAPRIN-1 proteins have high (approximately 85% or higher) sequence identity to the human or dog CAPRIN-1. The CAPRIN-1 whose expression level is to be measured in the method of the present invention may be, but not particularly limited to, a protein having preferably 85% or higher, more preferably 95% or higher sequence identity to the amino acid sequence of the dog or human CAPRIN-1 shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, or 14.

**[0026]** An antigenic substance, such as a protein, which has a complicated structure with a large molecular weight, usually contains a plurality of epitopes differing in structure on its molecule. Thus, plural types of antibodies that respectively recognize and bind to a plurality of epitopes on such an antigenic substance are produced *in vivo.* In other words, antibodies produced *in vivo* against the antigenic substance (e.g., protein) are polyclonal antibodies, which are mixtures of plural types of antibodies. The antibodies found by the present inventors to be specifically present in serum derived from cancer-affected organisms and to specifically bind to recombinant CAPRIN-1 through antigen-antibody reaction are also polyclonal antibodies. The term "polyclonal antibody" used in the present invention refers to an antibody that is found in serum derived from an organism containing an antigenic substance in the body, and has been induced in the organism against the antigenic substance.

**[0027]** Specific examples of a preferred polypeptide for use as an antigen for obtaining an anti-CAPRIN-1 antibody include polypeptides of even-numbered SEQ ID NOs of SEQ ID NOs: 2 to 28 and fragments thereof. Particularly, an anti-CAPRIN-1 antibody that is obtained using, as an antigen, the polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, or 28 or a fragment thereof comprising the amino acid sequence shown in SEQ ID NO: 66 containing a preferred epitope and specifically binds to (i.e., has immunological reactivity with) a polypeptide having the amino acid sequence shown in SEQ ID NO: 66 can be preferably used in the method of the present invention.

**[0028]** The nucleotide sequences of polynucleotides encoding polypeptides consisting of the amino acid sequences shown in even-numbered SEQ ID NOs of SEQ ID NOs: 2 to 30 (i.e., SEQ ID NOs: 2, 4, 6, ... 28, and 30) are shown in odd-numbered SEQ ID NOs of SEQ ID NOs: 1 to 29 (i.e., SEQ ID NOs: 1, 3, 5,... 27, and 29), respectively.

**[0029]** It is widely known to those skilled in the art that even a protein derived from a protein antigen by the substitution, deletion, addition, or insertion of a small number of amino acid residues in the amino acid sequence of the protein may generally have almost the same antigenicity as that of the original protein. Thus, a polypeptide having a sequence derived from the amino acid sequence of CAPRIN-1 by the substitution, deletion, addition and/or insertion of a small number of (preferably 1 or several) amino acid residues can also be used in the production of an anti-CAPRIN-1 antibody, as with the polypeptides consisting of the amino acid sequences shown in even-numbered SEQ ID NOs of SEQ ID NOs: 2 to 30, as long as the polypeptide has 80% or higher or 85% or higher, preferably 90% or higher, more preferably 95% or higher, further preferably 98% or higher sequence identity to the original sequence and specifically binds to a polyclonal antibody against CAPRIN-1 through antigen-antibody reaction (hereinafter, this polypeptide is also referred to as a "specifically-reactive modified polypeptide" for the sake of convenience). Preferably, the specifically-reactive modified polypeptide has an amino acid sequence derived from the amino acid sequence of CAPRIN-1 by the substitution, deletion, addition, and/or insertion of 1 or several amino acid residues. The term "several" used herein refers to an integer of 2 to 10, preferably an integer of 2 to 6, more preferably an integer of 2 to 4. The "sequence identity" used herein for the amino acid sequence refers to the percentage of a value determined by dividing the number of matched amino acid residues by the total number of amino acid residues in the best-matching alignments of the amino acid residues in two amino acid sequences to be compared. For the alignments, if necessary, one or both of these two sequences to be compared can be gapped. Such sequence alignments can be carried out using a well known program, for example, BLAST, FASTA, or CLUSTAL W (Karlin and Altschul, Proc. Natl. Acad. Sci. U.S.A., 87: 2264-2268, 1993; and Altschul et al., Nucleic Acids Res., 25: 3389-3402, 1997).

**[0030]** Twenty types of amino acids constituting a natural protein can be divided according to similar properties into the following groups: neutral amino acids having a low polar side chain (Gly, Ile, Val, Leu, Ala, Met, and Pro); neutral amino acids having a hydrophilic side chain (Asn, Gln, Thr, Ser, Tyr, and Cys); acidic amino acids (Asp and Glu); basic amino acids (Arg, Lys, and His); and aromatic amino acids (Phe, Tyr, Trp, and His). It is known that substitution within each of these groups, i.e., conservative substitution, does not change the properties of the polypeptide in most cases. Thus, in the case of substituting the amino acid residues of CAPRIN-1, a member in each of these groups can be substituted by another member in the same group so that the binding activity against the appropriate antibody is likely to be maintained. In the present invention, however, the modified form may have non-conservative substitution as long as the modified form is provided with immunity-inducing activity equivalent to or substantially equivalent to that of the unmodified form.

**[0031]** The polypeptide used in the present invention can be synthesized according to chemical synthesis methods, for example, Fmoc (fluorenylmethyloxycarbonyl) and tBoc (t-butyloxycarbonyl) methods (Seikagaku Jikken Koza (Biochemical Experimentation Course in English) 1, the Japanese Biochemical Society ed., Protein Chemistry IV, Chemical Modification and Peptide Synthesis, Tokyo Kagaku Dojin Co., Ltd. (Japan), 1981). Also, the polypeptide can be synthesized by routine methods using various commercially available peptide synthesizers. Alternatively, the polypeptide can be easily prepared using genetic engineering approaches known in the art (Sambrook et al., Molecular Cloning, the 2nd edition, Current Protocols in Molecular Biology (1989), Cold Spring Harbor Laboratory Press; Ausubel et al., Short Protocols in Molecular Biology, the 3rd edition, A compendium of Methods from Current Protocols in Molecular Biology (1995), John Wiley & Sons; etc.). For example, RNA is extracted from a tissue expressing a gene encoding the human CAPRIN-1 of SEQ ID NO: 2 or a homolog thereof. From this RNA, cDNA of the gene is prepared by RT-PCR. The full-length cDNA or a desired partial fragment thereof is incorporated into expression vectors, which can then be transferred to host cells to obtain the polypeptide of interest. The nucleotide sequences of cDNAs encoding the dog CAPRIN-1 proteins of SEQ ID NOs: 6, 8, 10, 12, and 14 are shown in SEQ ID NOs: 5, 7, 9, 11, and 13, respectively. The nucleotide sequences of cDNAs encoding the human CAPRIN-1 proteins of SEQ ID NOs: 2 and 4 as human homologs thereof are shown in SEQ ID NOs: 1 and 3, respectively. Primers for use in RT-PCR can therefore be easily designed with reference to these nucleotide sequences. As mentioned later, a gene encoding non-human mammalian CAPRIN-1 can be amplified with primers designed with reference to the nucleotide sequence of any odd-numbered SEQ ID NO of SEQ ID NOs: 5 to 29. Thus, cDNA encoding, for example, cat CAPRIN-1, can also be easily prepared by the same approach as above. The RNA extraction, RT-PCR, the incorporation of cDNA into vectors, and the transfer of the vectors to host cells can be carried out, for example, by well known methods as described below. Also, the vectors or host cells used are well known, and various products are commercially available.

**[0032]** The host cells may be any cell capable of expressing the above polypeptide. Examples of prokaryotic cells include *E. coli*. Examples of eukaryotic cells include: cultured mammalian cells such as monkey kidney cells COS1, Chinese hamster ovary cells CHO, a human embryonic kidney cell line HEK293, and mouse embryonic skin cell line NIH3T3; and budding yeast, fission yeast cells, silkworm cells, and *Xenopus* egg cells.

**[0033]** In the case of using prokaryotic cells as the host cells, the expression vectors used have an origin that permits replication in the prokaryotic cells, a promoter, a ribosomal binding site, a multicloning site, a terminator, a drug resistance gene, an auxotrophic complementary gene, etc. Examples of expression vectors for *E. coli* can include pUC series, pBluescript II, pET expression systems, and pGEX expression systems. DNA encoding the above polypeptide can be incorporated into such expression vectors, with which prokaryotic host cells are then transformed, followed by the culture of the obtained transformants so that the polypeptide encoded by the DNA is expressed in the prokaryotic host cells. In this respect, the polypeptide may be expressed as a fusion protein with an additional protein. In this context, the DNA encoding the above polypeptide can be obtained, for example, by the preparation of cDNA by RT-PCR as mentioned above. Alternatively, the DNA may be synthesized by routine methods using commercially available nucleic acid synthesizers as mentioned later. The nucleotide sequences of cDNAs of genes encoding the CAPRIN-1 proteins of SEQ ID NOs: 2 and 4 are shown in SEQ ID NOs: 1 and 3, respectively, in the Sequence Listing.

**[0034]** In the case of using eukaryotic cells as the host cells, expression vectors for eukaryotic cells having a promoter, a splicing region, a poly(A) addition site, etc. are used as the expression vectors. Examples of such expression vectors can include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pcDNA3, and pYES2 vectors. In the same way as above, the DNA encoding the above polypeptide used in the present invention can be incorporated into such expression vectors, with which eukaryotic host cells are then transformed, followed by the culture of the obtained transformants so that the polypeptide encoded by the DNA is expressed in the eukaryotic host cells. In the case of using expression vectors such as pIND/V5-His, pFLAG-CMV-2, pEGFP-N1, or pEGFP-C1, the polypeptide may be expressed as various fusion proteins tagged with His tag (e.g., $(\text{His})_6$ to $(\text{His})_{10}$), FLAG tag, myc tag, HA tag, GFP, or the like.

**[0035]** The expression vectors can be transferred to the host cells using well known methods such as electroporation, a calcium phosphate method, a liposome method, a DEAE dextran method, microinjection, viral infection, lipofection, and binding with cell-penetrating peptides.

**[0036]** The polypeptide of interest can be isolated and purified from the host cells by a combination of separation operations known in the art. Examples thereof include treatment with a denaturant (e.g., urea) or a surfactant, ultrasonication, enzymatic digestion, salting-out, solvent fractionation and precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing electrophoresis, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, and reverse-phase chromatography.

**[0037]** The polypeptides obtained by these methods also include their forms of fusion proteins with other arbitrary proteins. Examples thereof can include fusion proteins with glutathione-S-transferase (GST) or His tag. Such polypeptides in the form of fusion proteins are also encompassed by the specifically reactive added polypeptide mentioned above. The polypeptides expressed in transformed cells may undergo various intracellular modifications after translation. Such posttranslationally modified polypeptides may be used as long as these polypeptides have binding activity against the polyclonal antibody against CAPRIN-1. Examples of such posttranslational modifications can include N-terminal methionine elimination, N-terminal acetylation, glycosylation, intracellular protease-mediated limited degradation, myristoylation, isoprenylation, and phosphorylation.

**[0038]** The CAPRIN-1 as mentioned above or a fragment thereof can be used as an antigen to prepare an anti-CAPRIN-1 antibody. The anti-CAPRIN-1 antibody used in the present invention may be a polyclonal antibody or may be a monoclonal antibody. A monoclonal antibody is more preferred.

**[0039]** In the method of the present invention, an anti-CAPRIN-1 antibody specifically binding to (having immunological reactivity with) a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 66, among the anti-CAPRIN-1 antibodies obtained as mentioned above, can be preferably used in analysis such as the measurement of the expression level of CAPRIN-1. Such an anti-CAPRIN-1 antibody can bind to human or dog CAPRIN-1 (e.g., a polypeptide having the amino acid sequence shown in any even-numbered SEQ ID NO of SEQ ID NOs: 2 to 28) or a homolog thereof (e.g., a polypeptide having 85% or higher sequence identity to the polypeptide having the amino acid sequence shown in any even-numbered SEQ ID NO of SEQ ID NOs: 2 to 30) as a target.

**[0040]** The anti-CAPRIN-1 antibody having immunological reactivity with a polypeptide comprising the amino acid sequence shown in SEQ ID NO: 66 can be obtained as a polyclonal antibody by: immunizing an animal with the above CAPRIN-1 or a fragment thereof comprising the amino acid sequence shown in SEQ ID NO: 66; and screening the produced polyclonal antibodies for the immunological reactivity with the polypeptide of SEQ ID NO: 66. Alternatively, the anti-CAPRIN-1 antibody having immunological reactivity with a polypeptide comprising the amino acid sequence SEQ ID NO: 66 can also be obtained as a monoclonal antibody by: immunizing an animal with the above CAPRIN-1 or the fragment thereof; preparing monoclonal antibody-producing hybridomas using its immunocytes such as spleen cells; and further screening for an antibody having immunological reactivity with the polypeptide of SEQ ID NO: 66.

**[0041]** The animal to be immunized can be any non-human animal having spleen cells or the like that permit preparation of hybridoma cells. Examples thereof include mice, rats, hamsters, rabbits, and chickens. A mouse can be used more preferably.

**[0042]** The immunization method involves immunizing the animal with, for example, CAPRIN-1 or a fragment thereof conjugated with a carrier protein such as keyhole limpet hemocyanin (KLH), casein, or serum albumin as an immunogen together with an adjuvant to thereby induce an antibody against CAPRIN-1. More specifically, the above CAPRIN-1 or fragment thereof is subcutaneously or intraperitoneally administered several times together with an adjuvant to, for example, a 4- to 10-week-old mouse. After confirmation of an elevated antibody titer in blood, only CAPRIN-1 or a fragment thereof is intravenously or intraperitoneally administered to the mouse for a boost. At day 3 to 10, blood, ascites, or spleen cells can be collected. In this case, serum obtained from the collected blood, or the ascites contains polyclonal antibodies including anti-CAPRIN-1 antibodies. The obtained polyclonal antibodies can be screened by routine methods such as affinity chromatography for the binding to the polypeptide of SEQ ID NO: 66 to select an antibody having immunological reactivity with the polypeptide of SEQ ID NO: 66.

**[0043]** Examples of the adjuvant can include complete Freund's adjuvants, incomplete Freund's adjuvants, mixtures of aluminum hydroxide gel and pertussis vaccine, MPL + TDM adjuvant (Sigma-Aldrich Corp.), Titer Max Gold (Vaxel Inc.), and GERBU adjuvant (GERBU Biotechnik GmbH).

**[0044]** The antibody titer in blood can be measured by: collecting blood from the eye-ground venous plexus or tail vein of the immunized animal; and examining the presence or absence of the CAPRIN-1-reactive antibody in the obtained blood by an immunological assay method.

**[0045]** The spleen cells can be collected 3 to 10 days after boosting from the immunized animal which had been found to have an elevated antibody titer in blood and then boosted, and fused with myeloma cells to prepare hybridoma cells capable of growing autonomously. These hybridomas can be screened for hybridoma cells producing antibodies having the specificity of interest to prepare monoclonal antibodies in large amounts.

**[0046]** For the cell fusion, for example, SP2/0, P3-X63Ag8-U1 (P3-U1), P3-X63-Ag8653 (653), P3-X63-Ag8 (X63), or P3/NS1/1-Ag4-1 (NS1) can be used as the myeloma cells. These cell lines are available from, for example, ATCC (American Type Culture Collection), ECACC (European Collection of Cell Cultures), or Riken BioResource Center.

**[0047]** The cell fusion of the spleen cells with the myeloma cells can be carried out by: washing the cells of both lines; then mixing the myeloma cells and the spleen cells at a ratio of 1:1 to 10; and adding thereto polyethylene glycol or polyvinyl alcohol having an average molecular weight of 1000 to 6000 as a fusion promoter or using a commercially available cell fusion apparatus based on electrical stimulation (e.g., electroporation).

**[0048]** After the completion of the treatment for cell fusion, the fused cells are washed by suspension in a medium and cloned by a limiting dilution method or by a colony formation method in a methylcellulose medium. In this context, examples of the limiting dilution method can include a method which involves, for example, diluting the cells to $10^3$ to $10^7$ cells/mL and then inoculating the dilution at $10^2$ to $10^6$ cells/well to a 96-well microplate for cell culture, followed by the culture of the cells.

**[0049]** The culture medium for the hybridoma cell cloning is preferably supplemented with a HAT supplement in order to selectively obtain only the fused cells of interest. More specifically, the hybridoma cells of interest can be obtained and cloned according to the methods described in Antibodies: A Laboratory Manual (Cold Spring Harbor Laboratory, 1988) or Selected

Methods in Cellular Immunology (W.H. Freeman and Company, 1980).

**[0050]** The screen for the hybridoma cells producing the antibody having immunological reactivity with the polypeptide of SEQ ID NO: 66 can be performed for as follows: for example, CAPRIN-1 or a fragment thereof is immobilized onto a carrier, to which the culture supernatant (containing anti-CAPRIN-1 antibodies produced by the hybridoma cells) of each hybridoma cell line is then added. After reaction under conditions of 4 to 37°C for a time long enough to form an antibody/antigen complex, a secondary antibody labeled with, for example, an enzyme, a dye, or a radioisotope is contacted with the formed antibody/antigen complex and reacted under conditions of 4 to 37°C for a time long enough to form an antibody/antigen/secondary antibody complex. The presence or absence of the formed antibody/antigen/secondary antibody complex is further detected using a signal from the enzyme, dye, or radioisotope label on the secondary antibody as an indicator. An anti-CAPRIN-1 antibody confirmed to form the complex can be selected as the antibody of interest so that hybridoma cells producing this antibody of interest are screened for.

**[0051]** The hybridoma cells thus selected are used to condition a serum-free medium and monoclonal antibodies can be prepared from the resulting culture supernatant. For the large-scale preparation of monoclonal antibodies, for example, 0.5 mL of pristane (2,6,10,14-tetramethylpentadecane) is intraperitoneally administered to a 6- to 8-week-old nude mouse or SCID mouse. After rearing for 2 weeks, the hybridoma cells are intraperitoneally administered thereto at a dose of $5 \times 10^6$ to $2 \times 10^7$ cells/mouse. Monoclonal antibodies can be prepared from ascites generated by rearing for 10 to 21 days.

**[0052]** The thus-obtained anti-CAPRIN-1 antibody having immunological reactivity with the polypeptide having the amino acid sequence shown in SEQ ID NO: 66, or an antigen-binding fragment thereof can be used in the present invention. The antigen-binding fragment of the antibody means any antibody fragment that retains the ability to bind to the antigen. Examples thereof include Fv, scFv, Fab, Fab', and $F(ab)_2$. The anti-CAPRIN-1 antibody or the antigen-binding fragment may be conjugated with a metal such as manganese or iron.

**[0053]** In the method of the present invention, CAPRIN-1 that may be contained in the sample obtained from an organism (biological sample) is assayed. As mentioned above, cancer cells have been found to have a significantly high expression level (accumulation level) of CAPRIN-1 as an antigen. CAPRIN-1 itself can be assayed in cancer cells or cancer tissues to thereby determine the applicability of a CAPRIN-1-targeting drug to the patient having a high expression level of CAPRIN-1. This is as specifically described below in Examples.

**[0054]** The polypeptide in the biological sample can be easily assayed, as mentioned above, by a well known immunological assay method based on antigen-antibody reaction using the anti-CAPRIN-1 antibody or the antigen-binding fragment thereof. As mentioned above, not only the dog CAPRIN-1 of SEQ ID NO: 6 but its homologs in other mammals, for example, non-dog mammalian CAPRIN-1 (e.g., human CAPRIN-1 of SEQ ID NO: 2 or 4 or cat CAPRIN-1), can be assayed using an antibody capable of antigen-antibody reaction with, for example, the dog CAPRIN-1 of SEQ ID NO: 6, or an antigen-binding fragment thereof, due to cross-reactivity of the antibodies.

**[0055]** The organism from which the biological sample is derived or to which the method of the present invention is applied is a mammal and is preferably a human, a dog, or a cat.

**[0056]** Examples of the biological sample that is subjected to the method of the present invention typically include, but not limited to, body fluids, tissues, and cells. The "body fluid" used herein refers to a biological sample in a liquid state. Examples thereof include blood (including serum, plasma, and interstitial fluid), lymph, ascites, pleural effusion, spinal fluid, sputum, lacrimal fluid, nasal discharge, saliva, urine, vaginal fluid, and semen. The body fluid may additionally include, for example, peritoneal washings with saline. The body fluid used as the biological sample in the present invention is preferably serum, plasma, ascites, or pleural effusion.

**[0057]** For example, the expression level of CAPRIN-1 in the biological sample is measured using the anti-CAPRIN-1 antibody. If the expression level is higher (preferably, statistically significantly higher) than that of a healthy individual, this biological sample is indicated to contain cancer cells or cancer tissues. In the present invention, the "healthy individual" refers to a cancer-unaffected, normal individual of the same organism species as the test subject.

**[0058]** According to one embodiment, the anti-CAPRIN-1 antibody may be immunohistochemically tested for its reactivity with CAPRIN-1 in a tissue sample by an immunological assay method well known to those skilled in the art using a paraformaldehyde- or acetone-fixed frozen section or paraformaldehyde-fixed paraffin-embedded section of a tissue such as a tissue obtained from a patient during surgical operation or from an animal carrying a xenograft tissue inoculated with a cell line expressing CAPRIN-1 either spontaneously or after transfection.

**[0059]** The expression level (accumulation level or abundance) of CAPRIN-1 in the sample thus immunohistochemically stained can be quantitatively determined by numerical scoring based on staining patterns. Two or more scores are preferably set. In the most preferred aspect, the staining patterns are classified into 4 scores. For example, CAPRIN-1 expressed on the surface of cancer cells in a tissue sample is stained by a usual immunohistochemical staining method, and the amount thereof is given any of 4 scores reflecting its staining pattern. In such a case, each score is set as follows.

- Score 0 (without CAPRIN-1 overexpression): Positive staining of the cell membrane is not observed or is observed in less than 10% of the cancer cells.
- Score 1 (without CAPRIN-1 overexpression): Faint, almost unperceivable staining of the cell membrane is observed in 10% or more of the cancer cells, and these cancer cells are partially stained only at their cell membranes.
- Score 2 (with CAPRIN-1 overexpression): Weak to moderate complete positive staining

of the cell membrane is observed in 10% or more of the cancer cells, or strong complete positive staining of the cell membrane is observed in 10% or more and 30% or less of the cancer cells.

- Score 3 (with CAPRIN-1 overexpression): Strong complete positive staining of the cell membrane is observed in 30% or more of the cancer cells.

**[0060]** This score system is specified by American Society of Clinical Oncology (USA) and approved by The Japanese Society of Pathology (Japan). A similar scoring system is also exploited in "HercepTest" for quantitatively determining the abundance of a cancer antigen Her2 in samples of patients. The quantification of Her2 is specified by the ASCO/CAP Her2 testing guidelines. In Japan, a guideline for Her2 testing including this scoring system is also specified by the pathological committee for trastuzumab.

**[0061]** The ratio of stained cancer cells after immunohistochemical staining as indicated in each score can be determined by: counting at least 500 cells in the field of view using a light microscope with sensitivity increased to 4 times, 10 times, or 20 times; measuring cells that exhibit stain images of their cell membranes as described in each score; and making a trial calculation according to the following expression.

The number of positive cells / The total number of cells (approximately 500 cells) × 100

**[0062]** In these scoring criteria, biological samples with scores 2 and 3 can be determined to contain CAPRIN-1-expressing cancer tissues.

**[0063]** For the immunohistochemical staining, the antigen-antibody reaction of the anti-CAPRIN-1 antibody can be visualized by various methods. For example, the anti-CAPRIN-1 antibody is reacted with a secondary antibody labeled with an enzyme such as horseradish peroxidase or alkaline phosphatase, and the reaction (e.g., color reaction, chemiluminescence, or chemical fluorescence) of the enzyme can be induced to thereby visualize the binding of the anti-CAPRIN-1 antibody to CAPRIN-1. A fluorescent label, a radioisotope label, a biotin label, or the like can be used in the labeling of the secondary antibody.

**[0064]** CAPRIN-1 has been found to be a plasma membrane protein that is expressed on the surface of cancer cells. Since organisms contain many proteolytic enzymes, the extracellular region of CAPRIN-1 expressed on cancer cells in the body of a cancer patient is separated from the cancer cells upon degradation. The extracellular region thus separated is therefore present in larger amounts in the outside of the cells, compared with the intracellular region of CAPRIN-1. Accordingly, CAPRIN-1 present not only in cancer tissues but in body fluids or cell populations derived from cancer-affected individuals (e.g., cancer tissues fixed on slide glass or the serum of cancer patients) can be detected by the detection of CAPRIN-1 using an anti-CAPRIN-1 antibody or an antigen-binding fragment thereof capable of binding more strongly to the extracellular region of CAPRIN-1 present on the surface of cancer cells. Thus, in the present invention, an anti-CAPRIN-1 antibody binding to a portion expressed on the surface of cancer cells (CAPRIN-1 extracellular region) in the CAPRIN-1 protein is preferably used. Examples of the partial peptide of CAPRIN-1 recognized by such an antibody include partial peptides consisting of a sequence in extracellular regions in the amino acid sequences shown in even-numbered SEQ ID NOs of SEQ ID NOs: 2 to 30 in the Sequence Listing except for SEQ ID NOs: 6 and 18. Such sequence in these extracellular regions corresponds to a sequence of 7 or more consecutive amino acids in the region of amino acid residues (aa) 50 to 98 or amino acid residues (aa) 233 to 344 based on SEQ ID NO: 2 as a reference. Specifically, such a preferred anti-CAPRIN-1 antibody binds to a partial peptide of CAPRIN-1 comprising, for example, a sequence in the amino acid sequences of SEQ ID NOs: 43, 61, and 62 located in the extracellular region of CAPRIN-1 expressed on cancer cells. Also, an anti-CAPRIN-1 antibody particularly preferably used binds to a peptide comprising an amino acid sequence having 80% or higher, preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher sequence identity to any of these amino acid sequences. The anti-CAPRIN-1 antibody used in the method of the present invention, which specifically binds to (has immunological reactivity with) the polypeptide comprising the amino acid sequence shown in SEQ ID NO: 66, can bind to the extracellular region of CAPRIN-1. Thus, CAPRIN-1 can be detected with high sensitivity by use of the method of the present invention. The anti-CAPRIN-1 antibody specifically binding to (having immunological reactivity with) the polypeptide comprising the amino acid sequence shown in SEQ ID NO: 66 is further preferably an antibody (preferably a monoclonal antibody) having a heavy chain variable region comprising the amino acid sequence shown in SEQ ID NO: 70 and a light chain variable region comprising the amino acid sequence shown in SEQ ID NO: 71, or an antigen-binding fragment thereof.

**[0065]** The cancer to be detected by the method of the present invention is a cancer overexpressing CAPRIN-1 and examples thereof include, but not limited to, breast cancer, brain tumor, esophagus cancer, stomach cancer, lung cancer, liver cancer, kidney cancer, thyroid gland cancer, spleen cancer, pancreas cancer, large bowel cancer, skin cancer, ovary cancer, uterus cancer (uterine cervix cancer and uterine body cancer), prostate cancer, bladder cancer, testis cancer, and osteosarcoma. Other examples thereof can include, but not limited to, squamous cell cancer of the head and neck, melanoma, various types of adenocarcinomas, hepatocellular cancer, basal cell cancer, acanthoma-like gingival tumor, tumor mass in the oral cavity, perianal gland cancer, tumor mass of the anal sac, anal sac apocrine adenocarcinoma, Sertoli cell carcinoma, vaginal vestibule cancer, sebaceous cancer, sebaceous epithelioma, sebaceous adenoma, sweat gland cancer, adenocarcinoma in the nasal cavity, adenocarcinoma of the nose, bronchial adenocarcinoma, ducal cancer, mammary gland cancer, mammary complex carcinoma, malignant mixed tumor of the mammary gland, intraductal papillary adenocarcinoma, fibrosarcoma, hemangiopericytoma, chondrosarcoma, soft tissue sarcoma, histiocytic sarcoma, myxosarcoma, primitive sarcoma, lung cancer, mastocytoma, cutaneous leiomyoma, intraperitoneal leiomyoma, leiomyoma, chronic lymphocytic leukemia, lymphoma, gastrointestinal lymphoma, lymphoma of the digestive organ, small/medium cell lymphoma, adrenal medullary tumor, granulosa cell tumor, and pheochromocytoma.

**[0066]** In the method of the present invention, if the measured CAPRIN-1 expression level is higher (preferably, statistically significantly higher) than that of a healthy individual, the presence of a cancer that can be specifically bound by the anti-CAPRIN-1 antibody used in the measurement (i.e., a cancer that can be targeted by the antibody as a therapeutic drug for the cancer) in the organism (individual) from which the biological sample is derived, is indicated. Based on this, the expression level of CAPRIN-1 in a cancer patient-derived biological sample can be measured by the method of the present invention and compared with that of a healthy individual to determine whether a CAPRIN-1-targeting drug is applicable to the cancer in the patient (e.g., whether the cancer in the patient can be targeted by the antibody as a therapeutic drug for the cancer).

**[0067]** Thus, the present invention enables an identification of a cancer patient that can be expected to get therapeutic effects by the administration of a CAPRIN-1-targeting drug including a CAPRIN-1-targeting antibody, and thus the provision of more effective cancer treatment.

**[0068]** According to one embodiment, the present invention relates to a method for selecting an individual-specific therapeutic drug for a cancer, comprising: measuring the expression level of CAPRIN-1 in a biological sample using an antibody having immunological reactivity with a polypeptide having the amino acid sequence shown in SEQ ID NO: 66; and, if the expression level is higher (preferably, statistically significantly higher) than that of a healthy individual, selecting a CAPRIN-1-targeting drug, preferably an antibody having immunological reactivity with CAPRIN-1 or an antigen-binding fragment thereof, as a therapeutic drug for a cancer suitable for administration to the individual from which the biological sample is derived. This selection of the individual-specific therapeutic drug for a cancer realizes so-called tailor-made medicine, which offers cancer therapy optimized for an individual patient.

**[0069]** The term "statistically significantly" used herein means that statistically treated quantitative difference between the two is a significant difference. Specifically, examples thereof include the case where a significance level is smaller than 5%, 1%, or 0.1%. The method of verification is not particularly limited as long as the method is known in the art and is capable of determining the presence or absence of significance. For example, a Student's t test or multiple comparison test method can be used.

**[0070]** The present invention also provides a drug or kit for the diagnosis of a cancer, comprising, as a reagent, an anti-CAPRIN-1 antibody (particularly, an anti-CAPRIN-1 antibody having immunological reactivity with a polypeptide having the amino acid sequence shown in SEQ ID NO: 66) or an antigen-binding fragment thereof for use in the measurement of the expression of CAPRIN-1 according to the present invention. In this case, the drug or kit for the diagnosis of a cancer may further comprise, for example, various additives useful in the stabilization or the like of the antibody or the antigen-binding fragment. The anti-CAPRIN-1 antibody or the antigen-binding fragment may be conjugated with a metal such as manganese or iron. Such a metal-conjugated antibody or antigen-binding fragment, when administered to the body, accumulates to a site containing a larger amount of the antigenic protein.

Accordingly, the presence of cancer cells producing the antigenic protein can be detected by the MRI measurement or the like of the metal.

## Examples

**[0071]** Hereinafter, the present invention will be described more specifically with reference to Examples. However, the scope of the present invention is not intended to be limited by these Examples.

### Example 1: Analysis of CAPRIN-1 expression in each tissue

**[0072]** The expression of the CAPRIN-1 gene in dog and human normal tissues and various cancer tissues and cancer cell lines was examined by RT-PCR according to Example 1(4) of WO2010/016526. As a result, its strong expression was observed in the testis among the normal tissues of the healthy dog. Also, the expression was observed in dog breast cancer (Figure 1) and adenocarcinoma tissues. Further, the expression of the gene was also confirmed in human tissues. As a result, the expression was confirmed only in the testis among the normal tissues, as with the dog CAPRIN-1 gene, but was detected in many types of cancer cell lines including 8 human breast cancer cell lines (ZR75-1, MCF7, T47D, SK-BR-3, MDA-MB-157, BT-20, MDA-MB-231V, and MRK-nu-1) as well as a brain tumor cell line, a leukemia-derived cell line, a lung cancer cell line, and an esophagus cancer cell line (Figure 1). These results demonstrated that CAPRIN-1 is not expressed in normal tissues except for the testis, but is expressed in many cancer cells including breast cancer cells.

### Example 2: Preparation of antibody against CAPRIN-1

#### (1) Preparation of mouse anti-human CAPRIN-1 monoclonal antibody

**[0073]** 100 µg of human CAPRIN-1 having the amino acid sequence of SEQ ID NO: 2 as prepared in Example 3 of WO2010/016526 was mixed with an equal amount of MPL+TDM adjuvant (Sigma-Aldrich Corp.). This mixture was used as an antigen solution per mouse. This antigen solution was intraperitoneally administered to each 6-week-old Balb/c mouse (Japan SLC, Inc.). Then, 3 boosters were performed every 1 week. Three days after the final immunization, the spleen of the mouse was excised and ground between two sterilized glass slides. Procedures of washing with PBS(-) (Nissui Pharmaceutical Co., Ltd.) and removing the supernatant by centrifugation at 1500 rpm for 10 minutes were repeated three times to obtain spleen cells. The obtained spleen cells were mixed with mouse myeloma cells SP2/0 (purchased from ATCC) at a ratio of 10:1. 200 µL of an RPMI1640 medium containing 10% FBS was heated to 37°C and mixed with 800 µL of PEG1500 (Boehringer Ingelheim GmbH), and the PEG solution thus prepared was added to the cell mixture, which was then left standing for 5 minutes for cell fusion. After removal of the supernatant by centrifugation at 1700 rpm for 5 minutes, the cells were suspended in 150 ml of an RPMI1640 medium containing 15% FBS supplemented with 2% equivalent of a HAT solution (Life Technologies, Inc./Gibco) (HAT selective medium). This suspension was inoculated to fifteen 96-well plates (Nunc) at 100 µL/well. The spleen cells and the myeloma cells were fused by culture under conditions of at 37°C for 7 days in 5% $CO_2$ to obtain hybridomas.

**[0074]** The prepared hybridomas were screened for the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 as an indicator. The 1 µg/ml CAPRIN-1 protein solution was added to a 96-well plate at 100 µL/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% bovine serum albumin (BSA) solution (Sigma-Aldrich Corp.) was added thereto at 400 µL/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400 µL of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at 100 µL/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-mouse IgG (H+L) antibodies (Life Technologies, Inc.) diluted 5000-fold with PBS were added thereto at 100 µL/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (Thermo Fisher Scientific Inc.) was added thereto at 100 µL/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, several hybridomas producing antibodies having high absorbance were selected as candidate lines of the hybridoma of interest.

**[0075]** The selected hybridomas were added to a 96-well plate at a density of 0.5 cells/well and cultured in the plate. One week later, hybridomas forming single colonies in the wells were observed. The cells in these wells were further cultured, and the cloned hybridomas were screened for the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 as an indicator. The 1 µg/ml CAPRIN-1 protein solution was added to a 96-well plate at 100 µL/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% BSA solution was added thereto at 400 µL/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400 µL of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at 100 µL/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-mouse IgG (H+L) antibodies (Life Technologies, Inc.) diluted 5000-fold with PBS were added thereto at 100 µL/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (Thermo Fisher Scientific Inc.) was added thereto at 100 µL/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, a plurality of hybridoma lines producing monoclonal antibodies reactive with CAPRIN-1 were obtained. The culture supernatants of these hybridomas were purified using a protein G carrier and 150 types of monoclonal antibodies binding to CAPRIN-1 were obtained.

**[0076]** Next, these monoclonal antibodies were screened for the reactivity with the surface of breast cancer cells expressing CAPRIN-1. Specifically, $10^6$ cells of a human breast cancer cell line MDA-MB-231V were centrifuged in a 1.5-ml microcentrifuge tube. 100 µL of the supernatant of each hybridoma obtained above was added thereto and left standing for 1 hour on ice. After washing with PBS, FITC-labeled goat anti-mouse IgG antibodies (Life Technologies, Inc.) diluted 500-fold with PBS containing 0.1% fetal bovine serum were added thereto and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed with the addition of a medium instead of the antibodies as a control. As a result, 10 monoclonal antibodies (#1 to #10) having stronger fluorescence intensity than that of the control, i.e., reactive with the surface of breast cancer cells, were selected. The respective sequences of the heavy chain and light chain variable regions of these monoclonal antibodies are shown in SEQ ID NOs: 44 to 60. The monoclonal antibody #1 comprises the heavy chain variable region of SEQ ID NO: 44 and the light chain variable region of SEQ ID NO: 45; the monoclonal antibody #2 comprises the heavy chain variable region of SEQ ID NO: 44 and the light chain variable region of SEQ ID NO: 46; the monoclonal antibody #3 comprises the heavy chain variable region of SEQ ID NO: 44 and the light chain variable region of SEQ ID NO: 47; the monoclonal antibody #4 comprises the heavy chain variable region of SEQ ID NO: 44 and the light chain variable region of SEQ ID NO: 48; the monoclonal antibody #5 comprises the heavy chain variable region of SEQ ID NO: 49 and the light chain variable region of SEQ ID NO: 50; the monoclonal antibody #6 comprises the heavy chain variable region of SEQ ID NO: 51 and the light chain variable region of SEQ ID NO: 52; the monoclonal antibody #7 comprises the heavy chain variable region of SEQ ID NO: 53 and the light chain variable region of SEQ ID NO: 54; the monoclonal antibody #8 comprises the heavy chain variable region of SEQ ID NO: 55 and the light chain variable region of SEQ ID NO: 56; the monoclonal antibody #9 comprises the heavy chain variable region of SEQ ID NO: 57 and the light chain variable region of SEQ ID NO: 58; and the monoclonal antibody #10 comprises the heavy chain variable region of SEQ ID NO: 59 and the light chain variable region of SEQ ID NO: 60.

### (2) Identification of peptide in CAPRIN-1 bound by mouse anti-CAPRIN-1 antibody reactive with cancer cell surface

**[0077]** The cancer cell surface-reactive mouse anti-CAPRIN-1 monoclonal antibodies #1 to #10 obtained above were used to identify partial sequences in CAPRIN-1 recognized thereby.

**[0078]** First, DTT (Fluka) was added at a final concentration of 10 mM to 100 µL of a 1 µg/µL protein solution of recombinant CAPRIN-1 dissolved in PBS, and reacted at 95°C for 5 minutes to reduce disulfide bonds in the CAPRIN-1 proteins. Next, 20 mM (final concentration) iodoacetamide (Wako Pure Chemical Industries, Ltd.) was added thereto, followed by the alkylation reaction of thiol groups at 37°C for 30 minutes under shading conditions. 50 µg each of the mouse anti-CAPRIN-1 monoclonal antibodies #1 to #10 was added to 40 µg of the obtained reduced alkylated CAPRIN-1 proteins. The total amount of each mixture was adjusted to 1 mL with a 20 mM phosphate buffer (pH 7.0). The resulting mixture was reacted overnight at 4°C while mixed by stirring.

**[0079]** Next, trypsin (Promega K.K.) was added at a final concentration of 0.2 µg to each reaction mixture and reacted at 37°C for 1 hour, 2 hours, 4 hours, or 12 hours. Then, the reaction mixture was mixed with protein A-glass beads (GE Healthcare Bio-Sciences Ltd.) blocked with PBS containing 1% BSA (Sigma-Aldrich Corp.) and washed with PBS in advance, 1 mM calcium carbonate, and NP-40 buffer (20 mM phosphate buffer (pH 7.4), 5 mM EDTA, 150 mM NaCl, 1% NP-40) and reacted for 30 minutes.

**[0080]** Each reaction solution was washed with a 25 mM ammonium carbonate buffer (pH 8.0), followed by the elution of antigen-antibody complexes using 100 µL of 0.1% formic acid. The eluate was analyzed by LC-MS using Q-TOF Premier (Waters-MicroMass). This analysis followed the protocol attached to the instrument.

**[0081]** As a result, the polypeptide of SEQ ID NO: 61 was identified as a partial CAPRIN-1 sequence recognized by all of the mouse anti-human CAPRIN-1 monoclonal antibodies #1 to #10. In the polypeptide of SEQ ID NO: 61, the peptide of SEQ ID NO: 62 was further identified as a partial sequence recognized by the monoclonal antibodies #1 to #4, #5 to #7, and #9. As a partial sequence peptide, the peptide of SEQ ID NO: 63 was further found to be recognized by the monoclonal antibody #10.

### (3) Preparation of chicken anti-human CAPRIN-1 monoclonal antibody

**[0082]** 300 µg of human CAPRIN-1 having the amino acid sequence of SEQ ID NO: 2 as prepared in Example 3 of WO2010/016526 was mixed with an equal amount of a complete Freund's adjuvant. This mixture was used as an antigen solution per chicken. The antigen solution was intraperitoneally administered to 7-week-old chickens. Then, 7 boosters were performed every 4 weeks to complete immunization. Four days after the final shot, the spleen of each chicken was excised and ground between two sterilized glass slides. Procedures of washing with PBS(-) (Nissui Pharmaceutical Co., Ltd.) and removing the supernatant by centrifugation at 1500 rpm for 10 minutes were repeated three times to obtain spleen cells. The obtained spleen cells were mixed with light chain-deficient chicken myeloma cells established from chickens by transformation using avian reticuloendotheliosis virus, at a ratio of 5:1. 200 µL of an IMDM medium containing 10% FBS was heated to 37°C and mixed with 800 µL of PEG1500 (Boehringer Ingelheim GmbH), and the PEG solution thus prepared was added to the cell mixture, which was then left standing for 5 minutes for cell fusion. After removal of the supernatant by centrifugation at 1700 rpm for 5 minutes, the cells were suspended in 300 ml of an IMDM medium containing 10% FBS supplemented with 2%

equivalent of a HAT solution (Gibco) (HAT selective medium). This suspension was inoculated to thirty 96-well plates (Nunc) at 100 µL/well. The spleen cells and the chicken myeloma cells were fused by culture at 37°C for 7 days in 5% $CO_2$ to obtain hybridomas.

**[0083]** The prepared hybridomas were screened for the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 proteins as an indicator. The 1 µg/ml CAPRIN-1 protein solution was added to a 96-well plate at 100 µL/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% bovine serum albumin (BSA) solution (Sigma-Aldrich Corp.) was added thereto at 400 µL/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400 µL of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at 100 µL/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-chicken IgY antibodies (Sigma-Aldrich Corp.) diluted 5000-fold with PBS were added thereto at 100 µL/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (Thermo Fisher Scientific Inc.) was added thereto at 100 µL/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, several hybridomas producing antibodies having high absorbance were selected as candidate lines of the hybridoma of interest.

**[0084]** The selected hybridomas were added to a 96-well plate at a density of 0.5 cells/well and cultured in the plate. One week later, hybridomas forming single colonies in the wells were observed. The cells in these wells were further cultured, and the cloned hybridomas were screened for the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 proteins as an indicator. The 1 µg/ml CAPRIN-1 protein solution was added to a 96-well plate at 100 µL/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% BSA solution was added thereto at 400 µL/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400 µL of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at 100 µL/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-chicken IgY antibodies (Sigma-Aldrich Corp.) diluted 5000-fold with PBS were added thereto at 100 µL/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (Thermo Fisher Scientific Inc.) was added thereto at 100 µL/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, a plurality of hybridoma lines producing monoclonal antibodies reactive with CAPRIN-1 proteins were obtained as candidate lines of the hybridoma of interest.

**[0085]** Next, these monoclonal antibodies were screened for the reactivity with the surface of breast cancer cells expressing CAPRIN-1. Specifically, 5 × $10^5$ cells of a human breast cancer cell line MDA-MB-231V were centrifuged in a 1.5-ml microcentrifuge tube. 100 µL of the culture supernatant of each hybridoma obtained above was added thereto and left standing for 1 hour on ice. After washing with PBS, FITC-labeled goat anti-chicken IgG (H+L) antibodies (SouthernBiotech) diluted 30-fold with PBS containing 0.1% FBS were added thereto and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using a medium for hybridoma culture to prepare a control sample. As a result, 1 monoclonal antibody (chicken anti-human CAPRIN-1 monoclonal antibody #11) having stronger fluorescence intensity than that of the control, i.e., reactive with the surface of breast cancer cells expressing CAPRIN-1, was selected.

**(4) Preparation of mouse-chicken chimeric recombinant antibody**

**[0086]** The gene amplification fragment of the heavy chain variable region (SEQ ID NO: 64) of the chicken anti-human CAPRIN-1 monoclonal antibody #11 obtained in the preceding paragraph (3) was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA4/myc-His vector (Life Technologies, Inc.) into which a chicken antibody-derived leader sequence and a mouse IgG1 H chain constant region have been inserted. Also, the gene amplification fragment of the light chain variable region (SEQ ID NO: 65) of the chicken anti-human CAPRIN-1 monoclonal antibody #11 was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA3.1/myc-His vector (Life Technologies, Inc.) into which a chicken antibody-derived leader sequence and a mouse IgG1 L chain constant region have been inserted.

**[0087]** Next, the recombinant vector having the gene insert of the heavy chain variable region of the chicken anti-human CAPRIN-1 monoclonal antibody #11 and the recombinant vector having the gene insert of the light chain variable region of the chicken anti-human CAPRIN-1 monoclonal antibody #11 were introduced into CHO-K1 cells (obtained from Riken Cell Bank). Specifically, $2 \times 10^5$ CHO-K1 cells were cultured in 1 ml of Ham's F12 medium (Life Technologies, Inc.) containing 10% FBS per well of a 12-well culture plate, and washed with PBS(-). Then, 1 ml of fresh Ham's F12 medium containing 10% FBS per well was added thereto. The vectors (250 ng each) dissolved in 30 µL of OptiMEM (Life Technologies, Inc.) was mixed with 30 µL of Polyfect transfection reagent (Qiagen N.V.), and this mixture was added to each well. The CHO-K1 cells cotransfected with the recombinant vectors were cultured in a Ham's F12 medium containing 10% FBS supplemented with 200 µg/ml Zeocin (Life Technologies, Inc.) and 200 µg/ml Geneticin (Roche Diagnostics K.K.) and then inoculated to a 96-well plate at a density of 0.5 cells/well to prepare a cell line stably producing a mouse-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #12 having the variable regions of the chicken anti-human CAPRIN-1 monoclonal antibody #11 and the constant regions of mouse IgG1. The prepared cell line was cultured for 5 days in a 150-$cm^2$ flask at a density of $5 \times 10^5$ cells/ml using 30 ml of a serum-free OptiCHO medium (Life Technologies, Inc.) to obtain a culture supernatant containing #12.

### (5) Identification of CAPRIN-1 epitope recognized by mouse-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #12

**[0088]** The cancer cell surface-reactive mouse-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #12 obtained in the paragraph (4) was used to identify a CAPRIN-1 epitope region recognized thereby. 100 µg of recombinant CAPRIN-1 proteins was dissolved in a protein inhibitor-free dissolving buffer and reacted with the mouse-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #12. To this solution, a digestive enzyme trypsin or chymotrypsin was added, followed by digestion reaction at a suitable temperature. After the reaction, a protein G Sepharose carrier was added thereto, then reacted, and precipitated by centrifugation operation. After removal of the supernatant, the carrier was washed with a dissolving buffer and PBS and dissolved in 0.1% formic acid, and the supernatant was recovered. The recovered supernatant sample was applied to a reverse-phase column (HLB Extraction Cartridge (Waters-OASIS)) to obtain an antibody-free sample solution. The obtained sample was subjected to reverse-phase liquid chromatography (Chromatography Nanosytem (KYA Technologies Corp.)) to recover a solution containing only peptides. The solution was introduced to a tandem-type mass spectrometer Quadrupole-TOF Mass Spectrometer (Waters-MicroMass) and analyzed by MS/MS to detect the peptides contained in the sample. As a result, a peptide consisting of the amino acid sequence of SEQ ID NO: 66 was identified as a partial CAPRIN-1 sequence recognized by the mouse-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #12. The chicken anti-CAPRIN-1 monoclonal antibody #11 has the same heavy chain and light chain variable regions as those of the mouse-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #12 and as such, recognizes this peptide consisting of the amino acid sequence of SEQ ID NO: 66 as a partial CAPRIN-1 sequence.

### (6) Preparation of human-chicken chimeric anti-human CAPRIN-1 antibody

**[0089]** The gene amplification fragment of the heavy chain variable region (SEQ ID NO: 64) of the chicken anti-human CAPRIN-1 monoclonal antibody #11 obtained in the preceding paragraph (3) was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA4/myc-His vector (Life Technologies, Inc.) into which a chicken antibody-derived leader sequence comprising SEQ ID NO: 67 and a human IgG1 H chain constant region comprising SEQ ID NO: 68 have been inserted. Also, the gene amplification fragment of the light chain variable region (SEQ ID NO: 65) of the chicken anti-human CAPRIN-1 monoclonal antibody #11 was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA3.1/myc-His vector (Life Technologies, Inc.) into which a chicken antibody-derived leader sequence comprising SEQ ID NO: 68 and a human IgGl L chain constant region comprising SEQ ID NO: 69 have been inserted.

**[0090]** Next, the recombinant vector having the gene insert of the heavy chain variable region of the chicken monoclonal antibody #11 and the recombinant vector having the gene insert of the light chain variable region of the chicken monoclonal antibody #11 were introduced into CHO-K1 cells (obtained from Riken Cell Bank). Specifically, $2 \times 10^5$ CHO-K1 cells were cultured in 1 ml of Ham's F12 medium (Life Technologies, Inc.) containing 10% FBS per well of a 12-well culture plate, and washed with PBS(-). Then, 1 ml of fresh Ham's F12 medium containing 10% FBS per well was added thereto. The vectors (250 ng each) dissolved in 30 µL of OptiMEM (Life Technologies, Inc.) was mixed with 30 µL of Polyfect transfection reagent (Qiagen N.V.), and this mixture was added to each well. The CHO-K1 cells cotransfected with the recombinant vectors were cultured in a Ham's F12 medium containing 10% FBS supplemented with 200 µg/ml Zeocin (Life Technologies, Inc.) and 200 µg/ml Geneticin (Roche Diagnostics K.K.) and then inoculated to a 96-well plate at a density of 0.5 cells/well to prepare a cell line stably producing a human-chicken chimeric anti-human CAPRIN-1 antibody #13 having the variable regions of the chicken anti-human CAPRIN-1 monoclonal antibody #11 and the constant regions of human IgG1. The prepared cell line was cultured for 5 days in a 150-$cm^2$ flask at a density of $5 \times 10^5$ cells/ml using 30 ml of a serum-free OptiCHO medium (Life Technologies, Inc.) to obtain a culture supernatant containing the antibody #13.

**(7) Preparation of mouse anti-human CAPRIN-1 monoclonal antibody #14**

**[0091]** In the same way as in the paragraph (1), a fusion protein of the amino acid sequence of SEQ ID NO: 66 identified in the paragraph (5) and a carrier protein KLH (keyhole limpet hemocyanin) was mixed as an immunogen with an equal amount of an adjuvant TiterMax Gold$^{(R)}$ (CytRx Corp.), and this mixture was subcutaneously administered at a dose of 20 µg/shot to each mouse at 7-day intervals. After administration with four shots in total, spleen cells were obtained from the mouse 3 days after the final immunization and fused with mouse myeloma cells in the same way as in the paragraph (1) to prepare hybridomas. Then, antibodies were screened using, as an indicator, the reactivity of each antibody contained in the culture supernatants of the prepared hybridomas with a 1 µg/ml CAPRIN-1 protein solutions prepared in Example 3 of WO2010/016526 or a fusion protein of the amino acid sequence of SEQ ID NO: 66 used as an immunogen and a carrier protein KLH. The 1 µg/ml CAPRIN-1 protein solution prepared in Example 3 of WO2010/016526 and the fusion protein (30 µg/ml) of the amino acid sequence of SEQ ID NO: 66 and a carrier protein KLH were separately added at 100 µL/well to 96-well plates and left standing at 4°C for 18 hours. Each well was washed with PBS-T. Then, a Block Ace (DS Pharma Biomedical Co., Ltd.) solution was added thereto at 400 µL/well and left standing at room temperature for 3 hours. The solution in each well was removed, and each well was washed with PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at 100 µL/well and left standing at room temperature for 2 hours. Each well was washed with PBS-T. Then, HRP-labeled anti-mouse IgG (H+L) antibodies (Life Technologies, Inc.) diluted 5000-fold with PBS were added thereto at 100 µL/well and left standing at room temperature for 1 hour. Each well was washed with PBS-T. Then, a TMB substrate solution (Thermo Fisher Scientific Inc.) was added thereto at 100 µL/well and left standing for 5 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, hybridomas producing antibodies having high absorbance were selected.

**[0092]** The selected hybridomas were added to a 96-well plate at a density of 0.3 cells/well and cultured in the plate. One week later, hybridomas forming single colonies in the wells were observed. The cells in these wells were further cultured, and the cloned hybridomas were screened in the same way as above with the binding affinity of antibodies produced by the hybridomas to the amino acid sequence of SEQ ID NO: 66 as a partial CAPRIN-1 sequence as an indicator to obtain hybridomas producing antibodies against the amino acid of SEQ ID NO: 66.

**[0093]** Monoclonal antibodies produced by the obtained hybridomas were screened for the reactivity with the surface of breast cancer cells expressing CAPRIN-1. Specifically, $10^6$ cells of a human breast cancer cell line MDA-MB-231 were centrifuged in a 1.5-ml microcentrifuge tube. 100 µL of the culture supernatant of each hybridoma obtained above was added thereto and left standing for 1 hour on ice. After washing with PBS, FITC-labeled goat anti-mouse IgG antibodies (Life Technologies, Inc.) diluted 500-fold with PBS containing 0.1% FBS were added thereto and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using instead of the antibodies a sample of the serum of each untreated 6-week-old Balb/c mouse diluted 500-fold with a medium for hybridoma culture, or using secondary antibodies alone for reaction as a negative control. As a result, a mouse anti-human CAPRIN-1 monoclonal antibody #14 having stronger fluorescence intensity than that of the negative control, i.e., reactive with the surface of breast cancer cells, was obtained. The monoclonal antibody #14 comprises the heavy chain variable region of SEQ ID NO: 70 and the light chain variable region of SEQ ID NO: 71.

**[0094]** The obtained mouse anti-human CAPRIN-1 monoclonal antibody #14 was examined for its specific reaction with the amino acid sequence of SEQ ID NO: 66 that is a partial CAPRIN-1 sequence used as an immunogen. 30 µg/ml of a polypeptide consisting of the amino acid sequence of SEQ ID NO: 66 in a 0.1 M aqueous sodium carbonate solution and 30 µg/ml of a polypeptide consisting of a partial CAPRIN-1 sequence free from the amino acid sequence of SEQ ID NO: 66 in a 0.1 M aqueous sodium carbonate solution were separately added to 96-well plates Immobilizer Amino for ELISA (Nunc) at a concentration of 100 µg/ml and reacted all night and all day at 4°C to bind the peptides to the wells. A 0.1 M aqueous sodium carbonate solution containing 10 mM ethanolamine was added to the resulting peptide-bound well and left standing at room temperature for 1 hour. The solution in each well was removed, and each well was then washed with PBS-T. Then, a Block Ace solution was added thereto at 400 µL/well and left standing at room temperature for 3 hours. The solution in each well was removed, and each well was washed with PBS-T. Then, the culture supernatant containing the mouse monoclonal antibody #14 was added thereto at 50 µL/well and reacted at room temperature for

1 hour. Then, each well was washed with PBS-T, and HRP-labeled anti-mouse IgG (H+L) antibodies (Life Technologies, Inc.) diluted 5000-fold with a Block Ace solution were added thereto at 50 µL/well and left standing at room temperature for 1 hour. Each well was fully washed with PBS-T. Then, a TMB substrate solution (Thermo Fisher Scientific Inc.) was added thereto at 100 µL/well and left standing for 5 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 µL/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, the mouse monoclonal antibody #14 did not react with the partial CAPRIN-1 sequence free from the amino acid sequence of SEQ ID NO: 66, but specifically reacted only with the amino acid sequence of SEQ ID NO: 66. Thus, the polypeptide of SEQ ID NO: 66 was confirmed to contain an epitope region recognized by the mouse anti-human CAPRIN-1 antibody #14.

**Example 3: Analysis of CAPRIN-1 protein expression on cancer cell**

**[0095]** Next, 8 human breast cancer cell lines (ZR75-1, MCF7, T47D, SK-BR-3, MDA-MB-157, BT-20, MDA-MB-231V, and MRK-nu-1) confirmed to have a high rate of CAPRIN-1 gene expression were examined for their expression of CAPRIN-1 proteins on the cell surface. $5 \times 10^5$ cells of each human breast cancer cell line were centrifuged in a 1.5-ml microcentrifuge tube. 2 µg (5 µl) of the mouse-chicken anti-human CAPRIN-1 monoclonal antibody (#12) prepared in Example 2(4) was added thereto, further mixed by the addition of 95 µl of PBS containing 0.1% fetal bovine serum, and left standing for 1 hour on ice. After washing with PBS, the cells were mixed by the addition of 2 µl of Alexa 488-labeled goat anti-mouse IgG antibodies (Life Technologies, Inc.) and 98 µl PBS containing 0.1% fetal bovine serum (FBS) and left standing for 30 hours on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using mouse IgG1 instead of the mouse-chicken anti-human CAPRIN-1 monoclonal antibody (#12), as a control. As a result, the cancer cell lines supplemented with the mouse-chicken anti-human CAPRIN-1 monoclonal antibody (#12) all exhibited fluorescence intensity at least 35% stronger than that of the control. This demonstrated that CAPRIN-1 proteins are expressed on the cell membrane surface of the human cancer cell lines. The above rate of enhancement in fluorescence intensity was indicated by the rate of increase in mean fluorescence intensity (MFI) in each cell line and calculated according to the following expression.

Rate of increase in mean fluorescence intensity (Rate of enhancement in fluorescence intensity) (%) = ((MFI of cells reacted with the anti-CAPRIN-1 antibody) - (Control MFI)) / (Control MFI) × 100

**[0096]** Also, the fluorescence intensity was measured for 3 kidney cancer cell lines (Caki-1, Caki-2, and A498), a bladder cancer cell line (T24), an ovary cancer cell line (SKOV3), a lung cancer cell line (QG56), a prostate cancer cell line (PC3), a uterine cervix cancer cell line

(Hela), a fibrosarcoma cell line (HT1080), 2 brain tumor cell lines (T98G and U87MG), a gastric cancer cell line (MNK28), a large intestinal cancer cell line (Lovo), and pancreatic cancer cell lines (Capan-2, MIAPaCa-2, Panc-1, and BxPC-3) using the same approach as above. As a result, all the cancer cell lines had fluorescence intensity at least 35% stronger than that of the control.

**[0097]** As with the results obtained above, the CAPRIN-1 expression on cancer cell surface was also confirmed using the human-chicken chimeric anti-human CAPRIN-1 monoclonal antibody (#13) obtained in Example 2(6) or the mouse anti-human CAPRIN-1 monoclonal antibody (#14) obtained in Example 2(7).

## Example 4: Selection of optimum antibody for CAPRIN-1 detection

### (1) Selection of antibody using human breast cancer tissue

**[0098]** 31 breast cancer tissue samples of a paraffin-embedded human breast cancer tissue array (Medical & Biological Laboratories Co., Ltd.) were used in immunohistochemical staining. The human breast cancer tissue array was treated at 60°C for 3 hours and then placed in a staining bottle filled with xylene, and procedures of replacing xylene with a fresh one every 5 minutes were performed three times. Subsequently, the same operation as in xylene was performed using ethanol and PBS-T. The human breast cancer tissue array was placed in a staining bottle filled with a 10 mM citrate buffer solution (pH 6.0) containing 0.05% Tween 20, treated at 125°C for 5 minutes, and then left standing at room temperature for 40 minutes or longer. Excess water around a section was wiped off with a Kimwipe. The section on a glass slide was encircled with a Dako pen (Dako), and an appropriate amount of Peroxidase Block (Dako) was added dropwise thereto. The glass slide was left standing at room temperature for 5 minutes and then placed in a staining bottle filled with PBS-T, and procedures of replacing PBS-T with a fresh one every 5 minutes were performed three times. A PBS-T solution containing 10% FBS was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 µg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #8 or #14 prepared in Example 2 in a PBS-T solution containing 5% FBS was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS-T for 10 minutes three times, an appropriate amount of Peroxidase Labelled Polymer Conjugated (Dako) was added dropwise thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. After washing with PBS-T for 10 minutes three times, a DAB staining solution (Dako) was applied thereto, and the glass slide was left standing at room temperature for approximately 10 minutes. Then, the staining solution was discarded, and the glass slide was washed with PBS-T for 10 minutes three times. After rinsing with distilled water, the glass slide was placed in 70%, 80%, 90%, 95%, and 100% ethanol solutions in this order for 1 minute per solution, and finally left standing overnight in xylene. The glass slide was taken out and the section was embedded in Glycergel

Mounting Medium (Dako), followed by observation. The expression level of CAPRIN-1 in the tissues was evaluated according to the criteria given below. A slide that exhibited positive results was selected, and its CAPRIN-1 stain image was observed. First, the CAPRIN-1 stain image of cancer cells in the tissues, the intensity of positive staining, and the ratio of positive cells were observed by use of a × 4 objective lens of a light microscope. Next, the objective lens was changed to a × 10 or × 20 lens, and examination was made on whether the positive results were localized to the cell membrane or the cytoplasm. The detection results were evaluated in this way and classified into scores 0 to 3. The details of the scores are as follows.

- Score 0 (without CAPRIN-1 overexpression): Positive staining of the cell membrane is not observed or is observed in less than 10% of the cancer cells.
- Score 1 (without CAPRIN-1 overexpression): Faint, almost unperceivable staining of the cell membrane is observed in 10% or more of the cancer cells, and these cancer cells are partially stained only at their cell membranes.
- Score 2 (with CAPRIN-1 overexpression): Weak to moderate complete positive staining of the cell membrane is observed in 10% or more of the cancer cells, or strong complete positive staining of the cell membrane is observed in 10% or more and 30% or less of the cancer cells.
- Score 3 (with CAPRIN-1 overexpression): Strong complete positive staining of the cell membrane is observed in 30% or more of the cancer cells.

**[0099]** A cancer tissue was determined to be CAPRIN-1-positive, if its assay results were given score 2 or 3.

**[0100]** As a result, the expression of CAPRIN-1 in the breast cancer tissues was successfully confirmed using any of the antibodies. The results of immunohistochemical staining using the antibody #8 exhibited score 2 for 14 samples and score 3 for 1 sample, and therefore the number of CAPRIN-1-positive samples was 15 samples. The result of immunohistochemical staining using the antibody #14 exhibited score 2 for 18 samples and score 3 for 8 samples, and therefore the number of CAPRIN-1-positive samples was 26 samples. Thus, the antibody #14 was selected for the detection of CAPRIN-1 using human cancer tissues.

### (2) Detection of CAPRIN-1 on various human normal tissues by immunohistochemical staining method using antibody #14

**[0101]** A human normal tissue array (US Biomax, Inc.) (including brain, thyroid gland, lung, spleen, kidney, esophagus, stomach, large bowel, pancreas, muscle, skin, salivary gland, ovary, uterus, mammary gland, placenta, bone marrow, testis, and prostate tissues) was used in immunohistochemical staining. Excess water around a section was wiped off with a Kimwipe. The section on a glass slide was encircled with a Dako pen (Dako), and an appropriate amount of Peroxidase Block (Dako) was added dropwise thereto. The glass slide was left standing at room temperature for 5 minutes and then placed in a staining bottle filled with PBS-T, and procedures of replacing PBS-T with a fresh one every 5 minutes were performed three times. A PBS-T solution containing 10% FBS was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 µg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #14 prepared in Example 2 in a PBS-T solution containing 5% FBS was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS-T for 10 minutes three times, an appropriate amount of Peroxidase Labelled Polymer Conjugated (Dako) was added dropwise thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. After washing with PBS-T for 10 minutes three times, a DAB staining solution (Dako) was applied thereto, and the glass slide was left standing at room temperature for approximately 10 minutes. Then, the staining solution was discarded, and the glass slide was washed with PBS-T for 10 minutes three times. After rinsing with distilled water, the glass slide was placed in 70%, 80%, 90%, 95%, and 100% ethanol solutions in this order for 1 minute per solution, and finally left standing overnight in xylene. The glass slide was taken out and the section was embedded in Glycergel Mounting Medium (Dako), followed by observation.

**[0102]** The expression level of CAPRIN-1 in the tissues was evaluated according to the criteria given below. A slide that exhibited positive results was selected, and its CAPRIN-1 stain image was observed. First, the CAPRIN-1 stain image of cancer cells in the tissues, the intensity of positive staining, and the ratio of positive cells were observed by use of a × 4 objective lens of a light microscope. Next, the objective lens was changed to a × 10 or × 20 lens, and examination was made on whether the positive results were localized to the cell membrane or the cytoplasm. The detection results were evaluated in this way and classified into scores 0 to 3. The details of the scores are as follows.

- Score 0 (without CAPRIN-1 overexpression): Positive staining of the cell membrane is not observed or is observed in less than 10% of the cancer cells.
- Score 1 (without CAPRIN-1 overexpression): Faint, almost unperceivable staining of the cell membrane is observed in 10% or more of the cancer cells, and these cancer cells are partially stained only at their cell membranes.
- Score 2 (with CAPRIN-1 overexpression): Weak to moderate complete positive staining of the cell membrane is observed in 10% or more of the cancer cells, or strong complete positive staining of the cell membrane is observed in 10% or more and 30% or less of the cancer cells.
- Score 3 (with CAPRIN-1 overexpression): Strong complete positive staining of the cell membrane is observed in 30% or more of the cancer cells. A cancer tissue with score 2 or 3 was determined to be CAPRIN-1-positive.

**[0103]** The uterus and prostate tissues were given score 1, whereas the other tissues were all given score 0. Thus, the expression of CAPRIN-1 was not observed in the human normal tissues.

### (3) Detection of CAPRIN-1 protein on various human cancer tissues by immunohistochemical staining method using mouse anti-human CAPRIN-1 antibody #14

**[0104]** Various cancer tissues of a paraffin-embedded human cancer tissue array (US Biomax, Inc.) were used in immunohistochemical staining. The human cancer tissue array was treated at 60°C for 3 hours and then placed in a staining bottle filled with xylene, and procedures of replacing xylene with a fresh one every 5 minutes were performed three times. Subsequently, the same operation as in xylene was performed using ethanol and PBS-T. The human cancer tissue array was placed in a staining bottle filled with a 10 mM citrate buffer solution (pH 6.0) containing 0.05% Tween 20, treated at 125°C for 5 minutes, and then left standing at room temperature for 40 minutes or longer. Excess water around a section was wiped off with a Kimwipe. The section on a glass slide was encircled with a Dako pen (Dako), and an appropriate amount of Peroxidase Block (Dako) was added dropwise thereto. The glass slide was left standing at room temperature for 5 minutes and then placed in a staining bottle filled with PBS-T, and procedures of replacing PBS-T with a fresh one every 5 minutes were performed three times. A PBS-T solution containing 10% FBS was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 µg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #14 prepared in Example 2 in a PBS-T solution containing 5% FBS was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS-T for 10 minutes three times, an appropriate amount of Peroxidase Labelled Polymer Conjugated (Dako) was added dropwise thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. After washing with PBS-T for 10 minutes three times, a DAB staining solution (Dako) was applied thereto, and the glass slide was left standing at room temperature for approximately 10 minutes. Then, the staining solution was discarded, and the glass slide was washed with PBS-T for 10 minutes three times. The glass slide was rinsed with distilled water and placed in 70%, 80%, 90%, 95%, and 100% ethanol solutions in this order for 1 minute per solution, and finally left standing overnight in xylene. The glass slide was taken out and the section was embedded in Glycergel Mounting Medium (Dako), followed by observation.

**[0105]** The expression level of CAPRIN-1 in the tissues was evaluated according to the criteria given below. A slide that exhibited positive results was selected, and its CAPRIN-1 protein stain image was observed. First, the CAPRIN-1 stain image of cancer cells in the tissues, the intensity of positive staining, and the ratio of positive cells were observed by use of a × 4 objective lens of a light microscope. Next, the objective lens was changed to a × 10 or × 20 lens, and examination was made on whether the positive results were localized to the cell membrane or the cytoplasm. The detection results were evaluated in this way and classified into scores 0 to 3. The details of the scores are as follows.

- Score 0 (without CAPRIN-1 overexpression): Positive staining of the cell membrane is not observed or is observed in less than 10% of the cancer cells.

- Score 1 (without CAPRIN-1 overexpression): Faint, almost unperceivable staining of the cell membrane is observed in 10% or more of the cancer cells, and these cancer cells are partially stained only at their cell membranes.
- Score 2 (with CAPRIN-1 overexpression): Weak to moderate complete positive staining of the cell membrane is observed in 10% or more of the cancer cells, or strong complete positive staining of the cell membrane is observed in 10% or more and 30% or less of the cancer cells.
- Score 3 (with CAPRIN-1 overexpression): Strong complete positive staining of the cell membrane is observed in 30% or more of the cancer cells.

**[0106]** A cancer tissue was determined to be CAPRIN-1-positive, if its assay results were given score 2 or 3.

**[0107]** As a result, CAPRIN-1 was shown to be positive in 16 out of 22 brain tumor tissue samples (64%), 19 out of 32 lung cancer tissue samples (59%), 18 out of 21 uterus cancer tissue samples (86%), 10 out of 16 esophagus cancer tissue samples (63%), 27 out of 30 kidney cancer tissue samples (90%), 14 out of 17 liver cancer tissue samples (82%), 11 out of 15 thyroid gland cancer tissue samples (73%), 10 out of 14 stomach cancer tissue samples (71%), 17 out of 19 pancreas cancer tissue samples (89%), 13 out of 13 prostate cancer tissue samples (100%), 12 out of 14 bladder cancer tissue samples (86%), 11 out of 14 large bowel cancer tissue samples (79%), 24 out of 30 skin cancer tissue samples (80%), and 16 out of 21 breast cancer tissue samples (76%).

### (4) Detection of CAPRIN-1 protein on dog breast cancer tissue by immunohistochemical staining method using mouse anti-human CAPRIN-1 antibody #14

**[0108]** 100 frozen breast cancer tissue samples of dogs pathologically diagnosed as malignant breast cancer were used in immunohistochemical staining. Each frozen dog breast cancer tissue was sliced into 10 to 20 µm sections using Cryostat (Leica Biosystems), mounted on a glass slide, and dried in air, together with the glass slide, for 30 minutes using a hair dryer to prepare a glass slide with a tissue slice mounted thereon. Next, the glass slide was placed in a staining bottle filled with PBS-T (saline containing 0.05% Tween 20), and procedures of replacing PBS-T with a fresh one every 5 minutes were performed three times. Excess water around a section was wiped off with a Kimwipe. The section on the glass slide was encircled with a Dako pen (Dako). Then, a PBS-T solution containing 10% fetal bovine serum was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 µg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #8 or #14 prepared in Example 2 in a blocking solution, and this solution was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS-T for 10 minutes three times, MOM biotin-labeled anti-IgG antibodies (Vectastain) diluted 250-fold with a blocking solution were applied thereto, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. After washing with PBS-T for 10 minutes three times, avidin-biotin ABC reagent (Vectastain) was applied thereto, and the glass slide was left standing at room temperature for 5 minutes in a moist chamber. After washing with PBS-T for 10 minutes three times, a DAB staining solution (10 mg of DAB + 10 µL of 30% $H_2O_2$/ 50 ml of 0.05 M Tris-HCl (pH 7.6)) was applied thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. The glass slide was rinsed with distilled water. A hematoxylin reagent (Dako) was applied thereto, and the glass slide was left standing at room temperature for 1 minute and then rinsed with distilled water. The glass slide was placed in 70%, 80%, 90%, 95%, and 100% ethanol solutions in this order for 1 minute per solution, and then left standing overnight in xylene. The glass slide was taken out and the section was embedded in Glycergel Mounting Medium (Dako), followed by observation. The expression level of CAPRIN-1 in the tissues was evaluated according to the criteria given below. A slide that exhibited positive results was selected, and its CAPRIN-1 stain image was observed. First, the CAPRIN-1 stain image of cancer cells in the tissues, the intensity of positive staining, and the ratio of positive cells were observed by use of a × 4 objective lens of a light microscope. Next, the objective lens was changed to a × 10 or × 20 lens, and examination was made on whether the positive results were localized to the cell membrane or the cytoplasm. The detection results were evaluated in this way and classified into scores 0 to 3. The details of the scores are as follows.

- Score 0 (without CAPRIN-1 overexpression): Positive staining of the cell membrane is not observed or is observed in less than 10% of the cancer cells.
- Score 1 (without CAPRIN-1 overexpression): Faint, almost unperceivable staining of the cell membrane is observed in 10% or more of the cancer cells, and these cancer cells are partially stained only at their cell membranes.
- Score 2 (with CAPRIN-1 overexpression): Weak to moderate complete positive staining of the cell membrane is observed in 10% or more of the cancer cells, or strong complete positive staining of the cell membrane is observed in 10% or more and 30% or less of the cancer cells.
- Score 3 (with CAPRIN-1 overexpression): Strong complete positive staining of the cell membrane is observed in 30% or more of the cancer cells.

**[0109]** A cancer-bearing dog tissue was determined to be CAPRIN-1-positive and to be expected to get effective therapeutic effects by the administration of a CAPRIN-1-targeting drug, if its assay results were given score 2 or 3.

**[0110]** As a result, the expression of CAPRIN-1 in the dog breast cancer tissues was successfully shown using any of the antibodies. Specifically, the results of immunohistochemical staining using the antibody #8 exhibited score 2 for 69 samples and score 3 for 11 samples, and thus the number of CAPRIN-1-positive samples was 80 samples (80%). The result of immunohistochemical staining using the antibody #14 exhibited score 2 for 46 samples and score 3 for 36 samples, and thus the number of CAPRIN-1-positive samples was 82 samples (82%).

### (5) Detection of CAPRIN-1 on cat breast cancer tissue by immunohistochemical staining method using mouse anti-human CAPRIN-1 antibody #14

**[0111]** 30 frozen breast cancer tissue samples of cats pathologically diagnosed as malignant breast cancer were used in immunohistochemical staining. Each frozen cat cancer tissue was sliced into 10 to 20 µm sections using Cryostat (Leica Biosystems), mounted on a glass slide, and dried in air, together with the glass slide, for 30 minutes using a hair dryer to prepare a glass slide with a tissue slice mounted thereon. Next, the glass slide was placed in a staining bottle filled with PBS-T (saline containing 0.05% Tween 20), and procedures of replacing PBS-T with a fresh one every 5 minutes were performed three times. Excess water around a section was wiped off with a Kimwipe. The section on the glass slide was encircled with a Dako pen (Dako). Then, a PBS-T solution containing 10% fetal bovine serum was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 µg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #8 or #14 prepared in Example 2 in a blocking solution was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS-T for 10 minutes three times, MOM biotin-labeled anti-IgG antibodies (Vectastain) diluted 250-fold with a blocking solution were applied thereto, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. After washing with PBS-T for 10 minutes three times, avidin-biotin ABC reagent (Vectastain) was applied thereto, and the glass slide was left standing at room temperature for 5 minutes in a moist chamber. After washing with PBS-T for 10 minutes three times, a DAB staining solution (10 mg of DAB + 10 µL of 30% $H_2O_2$/ 50 ml of 0.05 M Tris-HCl (pH 7.6)) was applied thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. The glass slide was rinsed with distilled water. A hematoxylin reagent (Dako) was applied thereto, and the glass slide was left standing at room temperature for 1 minute and then rinsed with distilled water. The glass slide was placed in 70%, 80%, 90%, 95%, and 100% ethanol solutions in this order for 1 minute per solution, and then left standing overnight in xylene. The glass slide was taken out and the section was embedded in Glycergel Mounting Medium (Dako), followed by observation. The expression level of CAPRIN-1 in the tissues was evaluated according to the criteria given below. A slide that exhibited positive results was selected, and its CAPRIN-1 stain image was observed. First, the CAPRIN-1 stain image of cancer cells in the tissues, the intensity of positive staining, and the ratio of positive cells were observed by use of a × 4 objective lens of a light microscope. Next, the objective lens was changed to a × 10 or × 20 lens, and examination was made on whether the positive results were localized to the cell membrane or the cytoplasm. The detection results were evaluated in this way and classified into scores 0 to 3. The details of the scores are as follows.

- Score 0 (without CAPRIN-1 overexpression): Positive staining of the cell membrane is not observed or is observed in less than 10% of the cancer cells.
- Score 1 (without CAPRIN-1 overexpression): Faint, almost unperceivable staining of the cell membrane is observed in 10% or more of the cancer cells, and these cancer cells are partially stained only at their cell membranes.

- Score 2 (with CAPRIN-1 overexpression): Weak to moderate complete positive staining of the cell membrane is observed in 10% or more of the cancer cells, or strong complete positive staining of the cell membrane is observed in 10% or more and 30% or less of the cancer cells.
- Score 3 (with CAPRIN-1 overexpression): Strong complete positive staining of the cell membrane is observed in 30% or more of the cancer cells.

**[0112]** A cancer-bearing cat tissue was determined to be CAPRIN-1-positive and to expected to get effective therapeutic effects by the administration of a CAPRIN-1-targeting drug, if its assay results were given score 2 or 3.

**[0113]** As a result, the expression of CAPRIN-1 in the cat breast cancer tissues was successfully shown using any of the antibodies. Specifically, the results of immunohistochemical staining using the antibody #8 exhibited score 2 for 20 samples and score 3 for 4 samples, and thus the number of CAPRIN-1-positive samples was 24 samples (80%). The result of immunohistochemical staining using the antibody #14 exhibited score 2 for 18 samples and score 3 for 9 samples, and thus the number of CAPRIN-1-positive samples was 27 samples (90%).

## Example 5: Correlation of CAPRIN-1 expression evaluated using cancer sample with antitumor effect of antibody against CAPRIN-1 - I

### (1) Detection of CAPRIN-1 by immunohistochemical staining method using cancer tissue derived from cancer-bearing mouse in which mouse cancer cells were transplanted

**[0114]** Two mouse-derived cancer cell lines (B16F10 and EMT-6) were subcutaneously transplanted (each for 5 mice) into the dorsal regions of 26 Balb/c mice (Japan SLC, Inc.) and grown until the size of tumor became approximately 7 mm in diameter. Three subjects were selected from each of these two mouse groups respectively having the 2 types of transplanted cancer cells. A tumor mass was excised from each mouse, cut open in PBS, and perfusion-fixed overnight in a 0.1 M phosphate buffer solution (pH 7.4) containing 4% paraformaldehyde (PFA). The perfusate was discarded. The tissue surface of each organ was rinsed with PBS. A PBS solution containing 10% sucrose was added to a 50-ml centrifuge tube, each cancer tissue was then placed therein and shaken at 4°C for 2 hours using a rotor. The solution was replaced with a PBS solution containing 20% sucrose, and the sample was left standing at 4°C until the cancer tissue was precipitated. Then, the solution was replaced with a PBS solution containing 30% sucrose, and the sample was left standing at 4°C until the cancer tissue was precipitated. The cancer tissue was taken out, and desired portions were cut off with a surgical knife. Next, OCT compound (Tissue Tek) was poured onto the tissue surface and spread over the surface. Then, the tissue was placed on Cryomold. The Cryomold was placed on dry ice to quickly freeze the tissue, then sliced into 10 to 20 µm sections using Cryostat (Leica Biosystems), mounted on a glass slide, and dried in air, together with the glass slide, for 30 minutes using a hair dryer to prepare a glass slide with a tissue slice mounted thereon. On the next day, the glass slide was washed with PBS(-) three times. PBS(-) containing 5% goat serum was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 µg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #8 or #14 prepared in Example 2 in a PBS(-) solution was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS(-) for 5 minutes five times, an appropriate amount of Peroxidase Labelled Polymer Conjugated (Dako) was added dropwise thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. After washing with PBS-T for 5 minutes six times, a DAB staining solution (Dako) was applied thereto, and the glass slide was left standing at room temperature for approximately 10 minutes. Then, the staining solution was discarded, and the glass slide was washed with PBS(-) for 5 minutes three times. Then, the section on the glass slide was embedded in Glycergel Mounting Medium (Dako), followed by observation. As a result of scoring as described in Example 4, the results of immunohistochemical staining using the antibody #8 exhibited score 1 both for the melanoma-derived cells B16F10 and for the breast cancer-derived cells EMT-6. Thus, CAPRIN-1 expression was not detected. On the other hand, the results of immunohistochemical staining using the antibody #14 exhibited score 1 for the cancer cells B16F10, but exhibited score 3 for the cancer cells EMT-6.

### (2) Antitumor effect of antibody against CAPRIN-1

**[0115]** The human-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #13 was studied for its antitumor effect using the cancer-bearing mice prepared in the preceding paragraph (1). Of the cancer-bearing mice in which each cancer cell line (B16F10 or EMT-6) was transplanted, 5 cancer-bearing mice in each group underwent the intraperitoneal administration of the antibody #13 at a dose of 200 µg (200 µL) per mouse. Then, the antibody was intraperitoneally administered at the same dose as above to each cancer-bearing mouse a total of 3 times for 2 days. The size of tumor was measured every day, and the antitumor effect of the antibody #13 was observed (study group). On the other hand, PBS(-) was administered instead of the antibody to the remaining 5 cancer-bearing mice, which were in turn used as a control group.

**[0116]** As a result of observing the antitumor effect, the tumor volumes of the cancer cell B16F10-transplanted mice in the study group receiving the antibody #13 were increased to approximately 150%, 200%, 370%, and 630% at days 4, 6, 8, and 11, respectively, with the tumor volume at the start of antibody administration defined as 100%. On the other hand, the tumor volumes of the cancer cell EMT-6-transplanted mice in the study group were reduced to 51% at day 4, approximately 31% at day 6, and 9% at day 8 with the tumor volume at the start of antibody administration defined as 100%, and their tumors were almost completely regressed by days 10 to 14. The tumor volumes of both tumor-transplanted mice in the control group receiving PBS(-) were increased to approximately 230%, 290%, 470%, and 800% at days 4, 6, 8, and 11, respectively.

**[0117]** From the results mentioned above, the results of measuring the expression of CAPRIN-1 using the antibody #8 were not shown to correlate with cancer therapeutic effects based on the antitumor activity of the antibody, whereas the results of measuring the expression of CAPRIN-1 using the antibody #14 were shown to correlate with cancer therapeutic effects based on the antitumor activity of the antibody. Specifically, the results of measuring the expression level of CAPRIN-1 using the antibody #14 exhibited score 3 for the EMT-6 transplant-derived cancer tissues, which indicates CAPRIN-1 overexpression, and pharmacological effects based on the antitumor activity of the administered antibody were shown. On the other hand, the results of measuring the expression level of CAPRIN-1 using the antibody #14 exhibited score 1 for the transplanted B16F10-derived cancer tissues, which indicates that the expression of CAPRIN-1 was not observed. In addition, the antibody #13 having antitumor activity did not produce pharmacological effects when administered to the cancer-bearing mice in which the cancer cells B16F10 were transplanted.

**[0118]** These results indicated that a cancer or an individual determined to have a high expression level of CAPRIN-1 in a cancer tissue by detection of CAPRIN-1 in the cancer tissue using the antibody #14 of the present invention specifically binding to CAPRIN-1, can get high therapeutic effects by administering the anti-CAPRIN-1 antibody according to the present invention, based on the antitumor effect of the antibody.

## Example 6: Correlation of CAPRIN-1 expression evaluated using cancer sample with antitumor effect of antibody against CAPRIN-1 - II

### (1) Detection of CAPRIN-1 by immunohistochemical staining method using cancer tissue derived from cancer-bearing mouse in which mouse cancer cells were transplanted

**[0119]** Two mouse-derived cancer cell lines (B16 and CT26) were subcutaneously transplanted (each for 5 mice) into the dorsal regions of 26 Balb/c mice (Japan SLC, Inc.) and grown until the size of tumor became approximately 7 mm in diameter. Three subjects were selected from each of these two mouse groups respectively having the 2 types of transplanted cancer cells. A tumor mass was excised from each mouse, cut open in PBS, and perfusion-fixed overnight in a 0.1 M phosphate buffer solution (pH 7.4) containing 4% paraformaldehyde (PFA). The perfusate was discarded. The tissue surface of each organ was rinsed with PBS. A PBS solution containing 10% sucrose was added to a 50-ml centrifuge tube, each cancer tissue was then placed therein and shaken at 4°C for 2 hours using a rotor. The solution was replaced with a PBS solution containing 20% sucrose, and the sample was left standing at 4°C until the cancer tissue was precipitated. Then, the solution was replaced with a PBS solution containing 30% sucrose, and the sample was left standing at 4°C until the cancer tissue was precipitated. The cancer tissue was taken out, and desired portions were cut off with a surgical knife. Next, OCT compound (Tissue Tek) was poured onto the tissue surface and spread over the surface. Then, the tissue was placed on Cryomold. The Cryomold was placed on dry ice to quickly freeze the tissue, then sliced into 10 to 20 μm sections using Cryostat (Leica Biosystems), mounted on a glass slide, and dried in air, together with the glass slide, for 30 minutes using a hair dryer to prepare a glass slide with a tissue slice mounted thereon. On the next day, the glass slide was washed with PBS(-) three times. PBS(-) containing 5% goat serum was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. Next, 10 μg/ml of the mouse anti-human CAPRIN-1 monoclonal antibody #8 or #14 prepared in Example 2 in a PBS(-) solution was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber. After washing with PBS(-) for 5 minutes five times, an appropriate amount of Peroxidase Labelled Polymer Conjugated (Dako) was added dropwise thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. After washing with PBS-T for 5 minutes six times, a DAB staining solution (Dako) was applied thereto, and the glass slide was left standing at room temperature for approximately 10 minutes. Then, the staining solution was discarded, and the glass slide was washed with PBS(-) for 5 minutes three times. Then, the section on the glass slide was embedded in Glycergel Mounting Medium (Dako), followed by observation. As a result of scoring as described in Example 4, the results of immunohistochemical staining using the antibody #8 exhibited score 0 for the melanoma cells B16 and score 1 for the large bowel cancer cells CT26. Thus, CAPRIN-1 expression was not detected. On the other hand, the results of immunohistochemical staining using the antibody #14 exhibited score 0 for the cancer cells B16, but exhibited score 2 and thus to be positive for the cancer cells CT26.

### (2) Antitumor effect of antibody against CAPRIN-1

**[0120]** The human-chicken chimeric anti-human CAPRIN-1 monoclonal antibody #13 was studied for its antitumor effect using the cancer-bearing mice prepared in the preceding paragraph (1). Of the cancer-bearing mice in which each cancer cell line (B16 or CT26) was transplanted, 5 cancer-bearing mice in each group underwent the intraperitoneal administration of the antibody #13 at a dose of 200 μg (200 μL) per mouse. Then, the antibody was intraperitoneally administered at the same dose as above to each cancer-bearing mouse a total of 3 times for 2 days. The size of tumor was measured every day, and the antitumor effect of the antibody #13 was observed (study group). On the other hand, PBS(-) was administered instead of the antibody to the remaining 5 cancer-bearing mice, which were in turn used as a control group.

**[0121]** As a result of observing the antitumor effect, the tumor volumes of the cancer cell B16-transplanted mice in the study group receiving the antibody #13 were increased to approximately 170%, 220%, 390%, and 680% at days 4, 6, 8, and 11, respectively, with the tumor volume at the start of antibody administration defined as 100%. On the other hand, the tumor volumes of the cancer cell CT26-transplanted mice in the study group were reduced to

65% at day 4, approximately 41% at day 6, and 17% at day 8 with the tumor volume at the start of antibody administration defined as 100%, and their tumors were almost completely regressed by days 10 to 14. The tumor volumes of both tumor-transplanted mice in the control group receiving PBS(-) were increased to approximately 230%, 290%, 470%, and 800% at days 4, 6, 8, and 11, respectively.

**[0122]** From the results mentioned above, the results of measuring the expression of CAPRIN-1 using the antibody #8 were not shown to correlate with cancer therapeutic effects based on the antitumor activity of the antibody, whereas the results of measuring the expression of CAPRIN-1 using the antibody #14 were shown to correlate with cancer therapeutic effects based on the antitumor activity of the antibody. Specifically, the results of measuring the expression level of CAPRIN-1 using the antibody #14 exhibited score 2 for the CT26 transplant-derived cancer tissues, which indicates CAPRIN-1 overexpression, and pharmacological effects based on the antitumor activity of the administered antibody were shown. On the other hand, the results of measuring the expression level of CAPRIN-1 using the antibody #14 exhibited score 0 for the transplanted B16-derived cancer tissues, which indicates that the expression of CAPRIN-1 was not observed. In addition, the antibody #13 having antitumor activity did not produce pharmacological effects when administered to the cancer-bearing mice in which the cancer cells B16 were transplanted.

**[0123]** These results indicated that a cancer or an individual determined to have a high expression level of CAPRIN-1 in a cancer tissue by detection of CAPRIN-1 in the cancer tissue using the antibody #14 of the present invention specifically binding to CAPRIN-1, can get high therapeutic effects by administering the anti-CAPRIN-1 antibody according to the present invention, based on the antitumor effect of the antibody.

## Industrial Applicability

**[0124]** The present invention can be utilized for the diagnosis of a cancer and for the determination of administration of a CAPRIN-1-targeting drug such as a CAPRIN-1-specific therapeutic drug.

## Free Text of Sequence Listing

**[0125]** SEQ ID NOs: 31 to 36, and 38 to 42: Primer

## SEQUENCE LISTING

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Gly Ser Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro
575                 580                 585                 590

cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat tac aat       2007
Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn
                595                 600                 605

agt cgt ggt gtg tct cgt gga ggc tcc cgt ggt gct aga ggc ttg atg       2055
Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met
            610                 615                 620

aat gga tac cgg ggc cct gcc aat gga ttc aga gga gga tat gat ggt       2103


Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly
        625                 630                 635

tac cgc cct tca ttc tct aac act cca aac agt ggt tat aca cag tct       2151
Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser
    640                 645                 650

cag ttc agt gct ccc cgg gat tac tct ggc tat caa cgg gat gga tat       2199
Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr
655                 660                 665                 670

cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga gcc       2247
Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala
                675                 680                 685

cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg caa       2295
Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln
            690                 695                 700

atg aac act cag caa gtg aat taa tctgattcac aggattatgt ttaatcgcca      2349
Met Asn Thr Gln Gln Val Asn
        705

aaaacacact ggccagtgta ccataatatg ttaccagaag agttattatc tatttgttct     2409

ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca ggactacaat     2469
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tgtcagcttt ctattacctg gatatggaag gaaactattt ttactctgca tgttctgtcc 2529

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gcaagattga cttttatgac attggataaa atctacaaat cagccctcga gttattcaat 2709

gataactgac aaactaaatt atttccctag aaaggaagat gaaaggagtg gagtgtggtt 2769

tggcagaaca actgcatttc acagcttttc cagttaaatt ggagcactga acgttcagat 2829

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cagcactgtt catctggcca aacaactgtg gttaaaaaca catgtaaaat gctttttaac 2949

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tggtactatc tatcattcct tatgacatgt acattgtctg tcactaatcc ttggattttg 3189

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tatttttaaa ggggtgcctc attatggggc agagaacttt tcaataagtc tcattaagat 4689

ctgaatcttg gttctaagca ttctgtataa tatgtgattg cttgtcctag ctgcagaagg 4749

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cctttttgttt ggtcaaatgc atattttagc agagtttcaa ggaaatgatt gtcacacatg    4809

tcactgtagc ctcttggtgt agcaagctca catacaaaat acttttgtat atgcataata    4869

taaatcatct catgtggata tgaaacttct tttttaaaac ttaaaaaggt agaatgttat    4929

tgattacctt gattagggca gttttatttc cagatcctaa taattcctaa aaaatatgga    4989

aaagtttttt ttcaatcatt gtaccttgat attaaaacaa atatccttta agtatttcta    5049

atcagttagc ttctacagtt cttttgtctc cttttatatg cagctcttac gtgggagact    5109

tttccactta aaggagacat agaatgtgtg cttattctca gaaggttcat taactgaggt    5169

gatgagttaa caactagttg agcagtcagc ttcctaagtg ttttaggaca tttgttcatt    5229

atattttccg tcatataact agaggaagtg gaatgcagat aagtgccgaa ttcaaaccct    5289

tcattttatg tttaagctcc tgaatctgca ttccacttgg gttgttttta agcattctaa    5349

attttagttg attataagtt agatttcaca gaatcagtat tgcccttgat cttgtccttt    5409

ttatggagtt aacggggagg aagacccctc aggaaaacga aagtaaattg ttaaggctca    5469

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taaaattaca ctagattaaa taatatgaaa gtc                                  5562
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<400> 2

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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
            20                  25                  30


Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala
        35                  40                  45


Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys
    50                  55                  60


Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu
65                  70                  75                  80


Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val
                85                  90                  95


Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu
            100                 105                 110


Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys
        115                 120                 125


Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys
    130                 135                 140
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Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly
145 150 155 160

Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro
165 170 175

Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu
180 185 190

Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu
195 200 205

His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro
210 215 220

Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu Arg Val
225 230 235 240

Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu
245 250 255

Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln Val
260 265 270

Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu
275 280 285

Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln
290 295 300

Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr
305 310 315 320

Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro
325 330 335

Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro
340 345 350

Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly
355 360 365

Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr
370 375 380

Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn
385 390 395 400

Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg
405 410 415

Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val
420 425 430

Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu
435 440 445

```
Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Ile

    450                 455                 460

Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala
465                 470                 475                 480

Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly
                485                 490                 495

Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro
            500                 505                 510

Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro
        515                 520                 525

Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser
    530                 535                 540

Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu
545                 550                 555                 560

Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser
                565                 570                 575

Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln
            580                 585                 590

Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg
        595                 600                 605

Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly
    610                 615                 620

Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg
625                 630                 635                 640

Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser Gln Phe
                645                 650                 655

Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln
            660                 665                 670

Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg
        675                 680                 685

Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn
    690                 695                 700

Thr Gln Gln Val Asn
705
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<212> DNA

<213> Homo sapiens

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ctctcggtgc agcgggacag ggcgaagcgg cctgcgccca cggagcgcgc gacactgccc     120

ggaagggacc gccacccttg ccccctcagc tgcccactcg tgatttccag cggcctccgc     180

gcgcgcacg atg ccc tcg gcc acc agc cac agc ggg agc ggc agc aag tcg     231
          Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser
          1               5                   10

tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg agt gag gcg gcc gcg       279
Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala
15                  20                  25                  30

gga gcc ggg gcc gcc gcg ccg gct tct cag cac ccc gca acc ggc acc       327
Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr
                35                  40                  45

ggc gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg atc gac       375
Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp
            50                  55                  60

aag aaa ctt cgg aac ctg gag aag aaa aag ggt aag ctt gat gat tac       423
Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr
        65                  70                  75

cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag ctg gat       471
Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp
    80                  85                  90

gcc gtt tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca aaa       519
Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys
95                  100                 105                 110

gaa tta cag agg agt ttc atg gca cta agt caa gat att cag aaa aca       567
Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr
                115                 120                 125

ata aag aag aca gca cgt cgg gag cag ctt atg aga gaa gaa gct gaa       615
Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu
            130                 135                 140

cag aaa cgt tta aaa act gta ctt gag cta cag tat gtt ttg gac aaa       663
Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys
        145                 150                 155

ttg gga gat gat gaa gtg cgg act gac ctg aaa caa ggt ttg aat gga       711
Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly


    160                 165                 170

gtg cca ata ttg tcc gaa gag gag ttg tca ttg ttg gat gaa ttc tat       759
Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr
175                 180                 185                 190

aag cta gta gac cct gaa cgg gac atg agc ttg agg ttg aat gaa cag       807
Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln
                195                 200                 205

tat gaa cat gcc tcc att cac ctg tgg gac ctg ctg gaa ggg aag gaa       855
Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu
            210                 215                 220
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aaa cct gta tgt gga acc acc tat aaa gtt cta aag gaa att gtt gag       903
Lys Pro Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu
        225                 230                 235

cgt gtt ttt cag tca aac tac ttt gac agc acc cac aac cac cag aat       951
Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn
    240                 245                 250

ggg ctg tgt gag gaa gaa gag gca gcc tca gca cct gca gtt gaa gac       999
Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp
255                 260                 265                 270

cag gta cct gaa gct gaa cct gag cca gca gaa gag tac act gag caa      1047
Gln Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln
                275                 280                 285

agt gaa gtt gaa tca aca gag tat gta aat aga cag ttc atg gca gaa      1095
Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu
            290                 295                 300

aca cag ttc acc agt ggt gaa aag gag cag gta gat gag tgg aca gtt      1143
Thr Gln Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val
        305                 310                 315

gaa acg gtt gag gtg gta aat tca ctc cag cag caa cct cag gct gca      1191
Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala
    320                 325                 330

tcc cct tca gta cca gag ccc cac tct ttg act cca gtg gct cag gca      1239
Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala
335                 340                 345                 350

gat ccc ctt gtg aga aga cag cga gta caa gac ctt atg gca caa atg      1287
Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met
                355                 360                 365

cag ggt ccc tat aat ttc ata cag gat tca atg ctg gat ttt gaa aat      1335
Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn
            370                 375                 380

cag aca ctt gat cct gcc att gta tct gca cag cct atg aat cca aca      1383
Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr
        385                 390                 395

caa aac atg gac atg ccc cag ctg gtt tgc cct cca gtt cat tct gaa      1431
Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu
    400                 405                 410

tct aga ctt gct cag cct aat caa gtt cct gta caa cca gaa gcg aca      1479


Ser Arg Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr
415                 420                 425                 430

cag gtt cct ttg gta tca tcc aca agt gag ggg tac aca gca tct caa       1527
Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln
                435                 440                 445

ccc ttg tac cag cct tct cat gct aca gag caa cga cca cag aag gaa       1575
Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu
            450                 455                 460

cca att gat cag att cag gca aca atc tct tta aat aca gac cag act       1623
Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr
        465                 470                 475

aca gca tca tca tcc ctt cct gct gcg tct cag cct caa gta ttt cag       1671
Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln
    480                 485                 490

gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta aat gca       1719
Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala
495                 500                 505                 510

gct cca ttc caa tcc atg caa acg gtg ttc aat atg aat gcc cca gtt       1767
Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val
                515                 520                 525
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cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag tac cag       1815
Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln
            530                 535                 540

gcc agt tat aac cag agc ttt tct agt cag cct cac caa gta gaa caa       1863
Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln
        545                 550                 555

aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act tac cat       1911
Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His
    560                 565                 570

ggt tcc cca gac cag tcc cat caa gtg act ggt aac cac cag cag cct       1959
Gly Ser Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro
575                 580                 585                 590

cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat tac aat       2007
Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn
                595                 600                 605

agt cgt ggt gtg tct cgt gga ggc tcc cgt ggt gct aga ggc ttg atg       2055
Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met
            610                 615                 620

aat gga tac cgg ggc cct gcc aat gga ttc aga gga gga tat gat ggt       2103
Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly
        625                 630                 635

tac cgc cct tca ttc tct aac act cca aac agt ggt tat aca cag tct       2151
Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser
    640                 645                 650

cag ttc agt gct ccc cgg gat tac tct ggc tat caa cgg gat gga tat       2199
Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr
655                 660                 665                 670

cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga gcc       2247
Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala
                675                 680                 685

cca cga ggt aat att ttg tgg tgg tga tcctagctcc taagtggagc             2294
Pro Arg Gly Asn Ile Leu Trp Trp
            690

ttctgttctg gccttggaag agctgttaat agtctgcatg ttaggaatac atttatcctt     2354

tccagacttg ttgctaggga ttaaatgaaa tgctctgttt ctaaaactta atcttggacc     2414

caaattttaa tttttgaatg atttaatttt ccctgttact atataaactg tcttgaaaac     2474

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gaatgagatt gaacatttat ataaatttat tattcctctt tcattttttt gaaacatgcc     2654

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gaaccattta gaagtgatag aactaatgga atttgcaatg ccttttggac ctctattagt     2774

gatataaata tcaagttatt tctgactttt aaacaaaact cccaaattcc taacttattg     2834

agctatactt aaaaaaaatt acaggtttag agagtttttt gtttttcttt tactgttgga     2894

aaactacttc ccattttggc aggaagttaa cctatttaac aattagagct agcatttcat     2954

gtagtctgaa attctaaatg gttctctgat ttgagggagg ttaaacatca aacaggtttc     3014

ctctattggc cataacatgt ataaaatgtg tgttaaggag gaattacaac gtactttgat     3074

ttgaatacta gtagaaactg gccaggaaaa aggtacattt ttctaaaaat taatggatca     3134

cttgggaatt actgacttga ctagaagtat caaaggatgt ttgcatgtga atgtgggtta     3194
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tgttctttcc caccttgtag catattcgat gaaagttgag ttaactgata gctaaaaatc     3254

tgttttaaca gcatgtaaaa agttatttta tctgttaaaa gtcattatac agttttgaat     3314

gttatgtagt ttctttttaa cagtttaggt aataaggtct gttttcattc tggtgctttt     3374

attaattttg atagtatgat gttacttact actgaaatgt aagctagagt gtacactaga     3434

atgtaagctc catgagagca ggtaccttgt ctgtcttctc tgctgtatct attcccaacg     3494

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<210> 4
<211> 694
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<400> 4

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            20                  25                  30

Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala
        35                  40                  45

Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys
    50                  55                  60

Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu
65                  70                  75                  80

Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val
                85                  90                  95

Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu
            100                 105                 110

Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys
        115                 120                 125

Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys
    130                 135                 140

Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly
145                 150                 155                 160

Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro
                165                 170                 175

Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu
            180                 185                 190

Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu
        195                 200                 205
```

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His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro
    210                 215                 220

Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu Arg Val
225                 230                 235                 240

Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu
                245                 250                 255

Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln Val
            260                 265                 270

Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu
        275                 280                 285

Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln
    290                 295                 300

Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr
305                 310                 315                 320

Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro
                325                 330                 335

Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro
            340                 345                 350

Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly
        355                 360                 365

Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr
    370                 375                 380

Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn
385                 390                 395                 400

Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg
                405                 410                 415

Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val
            420                 425                 430

Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu
        435                 440                 445

Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Ile
    450                 455                 460

Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala
465                 470                 475                 480

Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly
                485                 490                 495

Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro
            500                 505                 510
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Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro
        515                 520                 525

Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser
    530                 535                 540

Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu
545                 550                 555                 560

Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser
                565                 570                 575

Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln
            580                 585                 590

Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg
        595                 600                 605

Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly
    610                 615                 620

Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg
625                 630                 635                 640

Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser Gln Phe
                645                 650                 655

Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln
            660                 665                 670

Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg
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Gly Asn Ile Leu Trp Trp
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<211> 1605

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<220>

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<222> (46)..(1392)

<400> 5

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caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt      105
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
5                   10                  15                  20

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc    153
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
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Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
25 30 35

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg 201
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
40 45 50

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg 249
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
55 60 65

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc 297
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
70 75 80

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac 345
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
85 90 95 100

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca 393
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
105 110 115

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc 441
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
120 125 130

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca 489
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
135 140 145

gca cct aca gtt gaa gac cag gta gct gaa gct gag cct gag cca gca 537
Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
150 155 160

gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat gta aat 585
Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
165 170 175 180

aga caa ttt atg gca gaa aca cag ttc agc agt ggt gaa aag gag cag 633
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
185 190 195

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag 681
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
200 205 210

cag caa cct cag gct gcg tct cct tca gta cca gag ccc cac tct ttg 729
Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
215 220 225

act ccg gtg gct cag gca gat ccc ctt gtg aga aga cag cga gtc cag 777
Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
230 235 240

gac ctt atg gcg cag atg cag ggg ccc tat aat ttc ata cag gat tca 825
Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
245 250 255 260

atg ctg gat ttt gaa aac cag aca ctc gat cct gcc att gta tct gca 873
Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala

265 270 275

cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc 921
Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
280 285 290

cct cca gtt cat tct gaa tct aga ctt gct caa cct aat caa gtt cct 969
Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
295 300 305

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag 1017
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
310 315 320

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag 1065
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
325 330 335 340

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct 1113
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
345 350 355

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct 1161
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
360 365 370

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt 1209
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
375 380 385

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc 1257
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
390 395 400

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa 1305
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
405 410 415 420

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag 1353
Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
425 430 435

cct cac caa gta gaa caa aca gag gga tgc cgc aaa tga acactcagca 1402
Pro His Gln Val Glu Gln Thr Glu Gly Cys Arg Lys
440 445

agtgaattaa tctgattcac aggattatgt ttaaacgcca aaaacacact ggccagtgta 1462

ccataatatg ttaccagaag agttattatc tatttgttct ccctttcagg aaacttattg 1522

taaagggact gttttcatcc cataaagaca ggactacaat tgtcagcttt atattacctg 1582

gaaaaaaaaa aaaaaaaaaa aaa 1605

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<212> PRT
<213> Canis familiaris

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Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val
35 40 45

Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu
50 55 60

Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu
65 70 75 80

Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile
85 90 95

```
His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr
            100                 105                 110

Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn
        115                 120                 125

Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu
    130                 135                 140

Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu
145                 150                 155                 160

Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr
                165                 170                 175

Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly
            180                 185                 190

Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val
        195                 200                 205

Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu
    210                 215                 220

Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg
225                 230                 235                 240

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

Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala
            260                 265                 270

Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro
        275                 280                 285

Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro
    290                 295                 300

Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser
305                 310                 315                 320

Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser
                325                 330                 335

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

Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu
        355                 360                 365

Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro
    370                 375                 380

Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met
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385 390 395 400

Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro
405 410 415

Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser
420 425 430

Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Gly Cys Arg Lys
435 440 445

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<212> DNA
<213> Canis familiaris

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

ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg 96
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
20 25 30

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag 144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
35 40 45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag 192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
50 55 60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag 240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65 70 75 80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt 288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
85 90 95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat 336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
100 105 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt 384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
115 120 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt 432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
130 135 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc 480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145 150 155 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg 528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
165 170 175

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg 576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser

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Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc         624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac         672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca         720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc         768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca         816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

gca cct aca gtt gaa gac cag gta gct gaa gct gag cct gag cca gca         864
Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat gta aat         912
Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

aga caa ttt atg gca gaa aca cag ttc agc agt ggt gaa aag gag cag         960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag        1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

cag caa cct cag gct gcg tct cct tca gta cca gag ccc cac tct ttg        1056
Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

act ccg gtg gct cag gca gat ccc ctt gtg aga aga cag cga gtc cag        1104
Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365

gac ctt atg gcg cag atg cag ggg ccc tat aat ttc ata cag gat tca        1152
Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

atg ctg gat ttt gaa aac cag aca ctc gat cct gcc att gta tct gca        1200
Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc        1248
Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

cct cca gtt cat tct gaa tct aga ctt gct caa cct aat caa gtt cct        1296
Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag        1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag        1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct        1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct        1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
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Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt      1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc      1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe


        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa      1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag      1680
Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca      1728
Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act      1776
Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc      1824
Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt      1872
Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620

ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc      1920
Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac      1968
Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655

agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc      2016
Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
            660                 665                 670

tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag      2064
Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
        675                 680                 685

agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc      2112
Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro
    690                 695                 700

aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa              2154
Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
705                 710                 715

tctgattcac aggattatgt ttaaacgcca aaaacacact ggccagtgta ccataatatg    2214

ttaccagaag agttattatc tatttgttct ccctttcagg aaacttattg taaagggact    2274

gttttcatcc cataaagaca ggactacaat tgtcagcttt atattacctg gatatggaag    2334

gaaactattt ttattctgca tgttcttcct aagcgtcatc ttgagccttg cacatgatac    2394

tcagattcct caccccttgct taggagtaaa acataataca ctttacaggg tgatatctcc    2454

atagttattt gaagtggctt ggaaaaagca agattaactt ctgacattgg ataaaaatca    2514

acaaatcagc cctagagtta ttcaaatggt aattgacaaa aactaaaata tttcccttcg    2574


agaaggagtg gaatgtggtt tggcagaaca actgcatttc acagcttttc cggttaaatt    2634
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ggagcactaa acgtttagat gcataccaaa ttatgcatgg gcccttaata taaaaggctg    2694

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cgcttctgta cttaatgtga agtatttaga taccttttg  aacacttaac agtttcttct    2934

gacaatgact tttgtaagga ttggtactat ctatcattcc ttataatgta cattgtctgt    2994

cactaatcct cagatcttgc tgtattgtca cctaaattgg tacaggtact gatgaaaata    3054

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gcaccagtat gtgttttaga ttgatttccc tattttaggg aaatgacaga cagtagtttc    3234

agttctgatg gtataagcaa aacaaataaa acatgtttat aaaagttgta tcttgaaaca    3294

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ttcattgtta gacaactgga gtttttgctg gttttgtaac ctactaaaat ggataggctg    3834

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tgtttatttt aaaataaaat aagttcttga cttttctcat gtgtggttgt ggtacatcat    3954

attggaaggg ttatctgttt acttttgcaa atgagtattt ctcttgctag cacctcccgt    4014

tgtgcgcttt aaatgacatc tgcctgggat gtaccacaac catatgttag ctgtatttta    4074

tggggaatag ataaaatatt cgtggtttat tgggtaatcc ctagatgtgt atgcttacaa    4134

tcctatatat aaaactaaat                                                4154
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<210> 8
<211> 717
<212> PRT
<213> Canis familiaris

<400> 8

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1               5                   10                  15


Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
            20                  25                  30


Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45


His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
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```
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

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

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

Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

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

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

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
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        355                 360                 365

Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

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

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620

Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655
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Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
660 665 670

Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
675 680 685

Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro
690 695 700

Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
705 710 715

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<211> 4939
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(2109)

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1 5 10 15

ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg 96
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
20 25 30

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag 144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
35 40 45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag 192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
50 55 60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag 240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65 70 75 80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt 288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
85 90 95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat 336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
100 105 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt 384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
115 120 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt 432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
130 135 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc 480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145 150 155 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg 528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
165 170 175

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aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg         576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc         624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac         672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca         720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc         768

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

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca         816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

gca cct aca gtt gaa gac cag gta gct gaa gct gag cct gag cca gca         864
Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat gta aat         912
Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

aga caa ttt atg gca gaa aca cag ttc agc agt ggt gaa aag gag cag         960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag        1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

cag caa cct cag gct gcg tct cct tca gta cca gag ccc cac tct ttg        1056
Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

act ccg gtg gct cag gca gat ccc ctt gtg aga aga cag cga gtc cag        1104
Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365

gac ctt atg gcg cag atg cag ggg ccc tat aat ttc ata cag gat tca        1152
Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

atg ctg gat ttt gaa aac cag aca ctc gat cct gcc att gta tct gca        1200
Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc        1248
Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

cct cca gtt cat tct gaa tct aga ctt gct caa cct aat caa gtt cct        1296
Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag        1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag        1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct        1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
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465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct       1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa       1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag       1680
Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca       1728
Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act       1776
Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc       1824
Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt       1872
Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620

ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc       1920
Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac       1968
Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655

agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc       2016
Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
            660                 665                 670

tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag       2064
Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
        675                 680                 685

agt gga cca cgg gga gcc cca cga ggt aat att ttg tgg tgg tga           2109
Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn Ile Leu Trp Trp
    690                 695                 700

tcctagctcc taagtggagc ttctgttctg gccttggaag agctgttcca tagtctgcat     2169

gtaggttaca tgttaggaat acatttatca ttaccagact tgttgctagg gattaaatga     2229

aatgctctgt ttctaaaact tctcttgaac ccaaatttaa ttttttgaat gactttccct     2289

gttactatat aaattgtctt gaaaactaga acatttctcc tcctcagaaa aagtgttttt     2349

ccaactgcaa attattttc aggtcctaaa acctgctaaa tgtttttagg aagtacttac      2409

tgaaacattt ttgtaagaca tttttggaat gagattgaac atttatataa atttattatt     2469

attcctcttt catttttgaa catgcatatt atattttagg gtcagaaatc ctttaatggc     2529

caaataagcc atagttacat ttagagaacc atttagaagt gatagaacta actgaaattt     2589

caatgccttt ggatcattaa tagcgatata aatttcaaat tgtttctgac ttttaaataa     2649
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aacatccaaa atcctaacta acttcctgaa ctatatttaa aaattacagg tttaaggagt 2709

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tgacttcaga tgaaaatctg cttgaaggca aagcaaataa tatttgaaag aaaaaccaaa 3609

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tttgaacact taacagtttc ttctgacaat gacttttgta aggattggta ctatctatca 4509

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ttataaaagt tgtatcttga aacactggtg ttcaacagct agcagcttat gtggttcacc 4869

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ccatgcattg ttagtgtttc agattttatg gttatctcca gcagctgttt ctgtagtact     4929

tgcatttatc                                                            4939
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<210> 10
<211> 702
<212> PRT
<213> Canis familiaris

<400> 10

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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
            20                  25                  30

Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

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

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

Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu


    130                 135                 140

Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240
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Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365

Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

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

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540
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Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620

Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655

Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
            660                 665                 670

Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
        675                 680                 685

Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn Ile Leu Trp Trp
    690                 695                 700
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<210> 11

<211> 3306

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (1)..(2040)

<400> 11

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

ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg       96
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
            20                  25                  30

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag      144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag      192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag      240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
```

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65                  70                  75                  80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt     288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
                85                  90                  95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat     336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
            100                 105                 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt     384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt     432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc     480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg     528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg     576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc     624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac     672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca     720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc     768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca     816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

gca cct aca gtt gaa gac cag gta gct gaa gct gag cct gag cca gca     864
Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat gta aat     912
Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

aga caa ttt atg gca gaa aca cag ttc agc agt ggt gaa aag gag cag     960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag    1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

cag caa cct cag gct gcg tct cct tca gta cca gag ccc cac tct ttg    1056
Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

act ccg gtg gct cag gca gat ccc ctt gtg aga aga cag cga gtc cag    1104
Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365

gac ctt atg gcg cag atg cag ggg ccc tat aat ttc ata cag gat tca    1152
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```
Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

atg ctg gat ttt gaa aac cag aca ctc gat cct gcc att gta tct gca      1200
Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala


385                 390                 395                 400

cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc     1248
Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

cct cca gtt cat tct gaa tct aga ctt gct caa cct aat caa gtt cct     1296
Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag     1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag     1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct     1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct     1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt     1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc     1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa     1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag     1680
Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca     1728
Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act     1776
Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc     1824
Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt     1872
Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620

ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc     1920
Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac     1968

Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655

agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc      2016
Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
            660                 665                 670
```

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tat cag cgg gga tgc cgc aaa tga acactcagca agtgaattaa tctgattcac      2070
Tyr Gln Arg Gly Cys Arg Lys
        675

aggattatgt ttaaacgcca aaaacacact ggccagtgta ccataatatg ttaccagaag      2130

agttattatc tatttgttct ccctttcagg aaacttattg taaagggact gttttcatcc      2190

cataaagaca ggactacaat tgtcagcttt atattacctg gatatggaag gaaactattt      2250

ttattctgca tgttcttcct aagcgtcatc ttgagccttg cacatgatac tcagattcct      2310

caccccttgct taggagtaaa acataataca ctttacaggg tgatatctcc atagttattt     2370

gaagtggctt ggaaaaagca agattaactt ctgacattgg ataaaaatca acaaatcagc      2430

cctagagtta ttcaaatggt aattgacaaa aactaaaata tttcccttcg agaaggagtg      2490

gaatgtggtt tggcagaaca actgcatttc acagcttttc cggttaaatt ggagcactaa      2550

acgtttagat gcataccaaa ttatgcatgg gcccttaata taaaaggctg gctaccagct      2610

ttgacacagc actattcatc ctctggccaa acaactgtgg ttaaacaaca catgtaaatt      2670

gctttttaac agctgatact ataataagac aaagccaaaa tgcaaaaatt gggctttgat      2730

tggcactttt tgaaaaatat gcaacaaata tgggatgtaa tctggatggc cgcttctgta      2790

cttaatgtga agtatttaga taccttttttg aacacttaac agtttcttct gacaatgact     2850

tttgtaagga ttggtactat ctatcattcc ttataatgta cattgtctgt cactaatcct      2910

cagatcttgc tgtattgtca cctaaattgg tacaggtact gatgaaaata tctaatggat      2970

aatcataaca ctcttggtca catgtttttc ctgcagcctg aaggttttta aaagaaaaag      3030

atatcaaatg cctgctgcta ccaccctttt aaattgctat cttttgaaaa gcaccagtat      3090

gtgttttaga ttgatttccc tattttaggg aaatgacaga cagtagtttc agttctgatg      3150

gtataagcaa aacaaataaa acatgtttat aaaagttgta tcttgaaaca ctggtgttca      3210

acagctagca gcttatgtgg ttcaccccat gcattgttag tgtttcagat tttatggtta      3270

tctccagcag ctgtttctgt agtacttgca tttatc                                3306
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<210> 12

<211> 679

<212> PRT

<213> Canis familiaris

<400> 12

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

Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
            20                  25                  30

Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80
```

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 65                  70                  75                  80

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

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

Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

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

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

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser


            260                 265                 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365
```

```
Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

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

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620

Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655

Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
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            660                 665                 670

Tyr Gln Arg Gly Cys Arg Lys
        675
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<210> 13
<211> 2281
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(2154)

<400> 13

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atg ccg tcg gcc acc agc ctc agc gga agc ggc agc aag tcg tcg ggc        48
Met Pro Ser Ala Thr Ser Leu Ser Gly Ser Gly Ser Lys Ser Ser Gly
1                 5                   10                  15

ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg        96
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
             20                  25                  30

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag       144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
         35                  40                  45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag       192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
     50                  55                  60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag       240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
 65                  70                  75                  80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt       288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
                 85                  90                  95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat       336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
            100                 105                 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt       384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt       432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc       480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg       528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg       576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc       624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac       672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
```

```
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca       720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc       768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca       816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

gca cct aca gtt gaa gac cag gta gct gaa gct gag cct gag cca gca       864
Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat gta aat        912
Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

aga caa ttt atg gca gaa aca cag ttc agc agt ggt gaa aag gag cag        960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag       1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

cag caa cct cag gct gcg tct cct tca gta cca gag ccc cac tct ttg       1056
Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

act ccg gtg gct cag gca gat ccc ctt gtg aga aga cag cga gtc cag       1104
Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365

gac ctt atg gcg cag atg cag ggg ccc tat aat ttc ata cag gat tca       1152
Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

atg ctg gat ttt gaa aac cag aca ctc gat cct gcc att gta tct gca       1200
Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc       1248
Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

cct cca gtt cat tct gaa tct aga ctt gct caa cct aat caa gtt cct       1296
Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag       1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag       1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct       1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct       1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
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Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
515 520 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa 1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys

530 535 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag 1680
Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545 550 555 560

cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca 1728
Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
565 570 575

gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act 1776
Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
580 585 590

ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc 1824
Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
595 600 605

agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt 1872
Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
610 615 620

ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc 1920
Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625 630 635 640

aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac 1968
Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
645 650 655

agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc 2016
Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
660 665 670

tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag 2064
Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
675 680 685

agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc 2112
Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro
690 695 700

aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa 2154
Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
705 710 715

tctgattcac aggattatgt ttaaacgcca aaaacacact ggccagtgta ccataatatg 2214

ttaccagaag agttattatc tatttggact gttttcatcc cataaagaca ggactacaat 2274

tgtcagc 2281

<210> 14

<211> 717

<212> PRT

<213> Canis familiaris

<400> 14

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

Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
20 25 30

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Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

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

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

Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

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

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

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
        275                 280                 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
    290                 295                 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335
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Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
            340                 345                 350

Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
        355                 360                 365

Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
    370                 375                 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385                 390                 395                 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
                405                 410                 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
            420                 425                 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe

        515                 520                 525

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545                 550                 555                 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
                565                 570                 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
            580                 585                 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
        595                 600                 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
    610                 615                 620
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Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625                 630                 635                 640

Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn
                645                 650                 655

Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
            660                 665                 670

Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
        675                 680                 685

Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro
    690                 695                 700

Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
705                 710                 715
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ctctcccctt acggtttcaa g atg cct tcg gcc acc agc cac agc gga agc       111
                        Met Pro Ser Ala Thr Ser His Ser Gly Ser
                        1               5                   10

ggc agc aag tcg tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg aat       159
Gly Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Asn
                15                  20                  25

gag gcg ggg gcc ggg gcc gcc gcg ccg gct tcc caa cac ccc atg acc       207
Glu Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Met Thr
            30                  35                  40

ggc acc ggg gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg       255
Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val
        45                  50                  55

atc gac aag aaa ctt cgg aac ctg gag aag aaa aag ggc aag ctt gat       303
Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp
    60                  65                  70

gat tat cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag       351
Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln
75                  80                  85                  90

ctg gat gcc gtg tct aag tac cag gaa gtc aca aat aac ttg gag ttt       399
Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe
                95                  100                 105

gca aaa gaa tta cag agg agt ttc atg gca tta agc caa gat att cag       447
Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln
            110                 115                 120

aaa aca ata aag aag aca gca cgt cgg gag cag ctt atg aga gag gaa       495
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Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu
    125                     130                 135

gct gaa cag aaa cgt tta aaa aca gta ctt gag ctg cag tat gtt ttg        543
Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu
    140                 145                 150

gac aaa cta gga gat gat gaa gtg aga act gac ctg aag caa ggt ttg        591
Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu
155                 160                 165                 170

aat gga gtg cca ata ttg tct gaa gag gag ttg tcg ttg tta gat gag        639
Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu
                175                 180                 185

ttc tac aaa tta gca gac cct gaa cga gac atg agc ttg agg ttg aat        687
Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn
            190                 195                 200

gag cag tat gaa cat gcc tcc att cac ctg tgg gac ttg ctg gaa gga        735
Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly
        205                 210                 215

aag gaa aaa cct gta tgt gga aca act tat aaa gct cta aag gaa att        783
Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile
    220                 225                 230

gtt gag cgt gtt ttc cag tca aac tac ttt gac agc acc cac aac cac        831
Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His


235                 240                 245                 250

cag aat ggt ctg tgt gag gaa gag gag gca gcc tca gca cct aca gtt       879
Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val
                255                 260                 265

gaa gac cag gca gct gaa gct gaa cct gag cca gtg gaa gaa tat act       927
Glu Asp Gln Ala Ala Glu Ala Glu Pro Glu Pro Val Glu Glu Tyr Thr
            270                 275                 280

gaa caa aat gag gtt gaa tca aca gag tat gta aat aga caa ttt atg       975
Glu Gln Asn Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met
        285                 290                 295

gca gaa aca cag ttc agc agt ggt gaa aag gag cag gta gat gat tgg      1023
Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Asp Trp
    300                 305                 310

aca gtt gaa aca gtt gag gtg gta aat tca ctc cag cag caa cct cag      1071
Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln
315                 320                 325                 330

gct gca tct cct tca gta cca gaa ccc cac tct ttg acc cca gtg gct      1119
Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala
                335                 340                 345

caa gcc gat ccc ctc gtg aga aga cag cga gta cag gac ctt atg gca      1167
Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala
            350                 355                 360

caa atg cag ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt      1215
Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe
        365                 370                 375

gaa aac cag aca ctt gat cct gcc att gta tct gca cag ccg atg aat      1263
Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn
    380                 385                 390

cca gca cag aac atg gac ata ccc cag ctg gtt tgc cct cca gtt cat      1311
Pro Ala Gln Asn Met Asp Ile Pro Gln Leu Val Cys Pro Pro Val His
395                 400                 405                 410

tct gaa tct aga ctt gct caa cct aat caa gtt tct gta cag cca gaa      1359
Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Ser Val Gln Pro Glu
                415                 420                 425
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gct aca cag gtt cct ttg gtt tca tcc aca agt gag gga tat aca gca       1407
Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala
            430                 435                 440

tct caa ccc ttg tac caa cct tct cat gct act gac caa cga cca caa       1455
Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Asp Gln Arg Pro Gln
        445                 450                 455

aag gaa ccg att gat cag att cag gcg acg atc tct tta aat aca gac       1503
Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp
    460                 465                 470

cag act aca gca tca tca tcc ctt cct gct gct tct cag cct caa gtg       1551
Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val
475                 480                 485                 490

ttc cag gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta       1599


Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val
                495                 500                 505

aat gca gct cca ttc caa tcc atg caa acg gta ttc aat atg aat gcc       1647
Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala
            510                 515                 520

cca gtt cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag       1695
Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln
        525                 530                 535

tac cag gcc agt tac aac cag agc ttt tcc agt cag cct cac caa gta       1743
Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val
    540                 545                 550

gaa caa aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act       1791
Glu Gln Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr
555                 560                 565                 570

tat cat ggt tct cag gac cag ccc cat caa gtg act ggt aac cac cag       1839
Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr Gly Asn His Gln
                575                 580                 585

cag cct cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat       1887
Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr
            590                 595                 600

tac aac agt cgt ggt gtg tct cgt gga ggt tcc cgt ggt gct aga ggc       1935
Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly
        605                 610                 615

ttg atg aat gga tac aga gga cct gct aat gga ttc aga gga gga tat       1983
Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr
    620                 625                 630

gat ggt tac cgc cct tca ttc tct act aac act cca aac agt ggt tat       2031
Asp Gly Tyr Arg Pro Ser Phe Ser Thr Asn Thr Pro Asn Ser Gly Tyr
635                 640                 645                 650

aca caa tct caa ttc agt gct ccc cgg gac tac tct ggc tat cag cgg       2079
Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg
                655                 660                 665

gat gga tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca       2127
Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro
            670                 675                 680

cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg       2175
Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly
        685                 690                 695

atg ccg caa atg aac act cag caa gtg aat taa tctgattcac aggattatgt     2228
Met Pro Gln Met Asn Thr Gln Gln Val Asn
    700                 705

ttaatcgcca aaaacacact ggccagtgta ccataatatg ttaccagaag agttattatc     2288

tatttgttct ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca     2348
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ggactacaat tgtcagcttt atattacctg gatatggaag gaaactattt ttactctgca 2408

tgttctgtcc taagcgtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc 2468

ttaggagtaa aacataatat actttaatgg ggtgatatct ccatagttat ttgaagtggc 2528

ttggataaag caagactgac ttctgacatt ggataaaatc tacaaatcag ccctagagtc 2588

attcagtggt aactgacaaa actaaaatat ttcccttgaa aggaagatgg aaggagtgga 2648

gtgtggtttg gcagaacaac tgcatttcac agcttttcca cttaaattgg agcactgaac 2708

atttagatgc ataccgaatt atgcatgggc cctaatcaca cagacaaggc tggtgccagc 2768

cttaggcttg acacggcagt gttcaccctc tggccagacg actgtggttc aagacacatg 2828

taaattgctt tttaacagct gatactgtat aagacaaagc caaaatgcaa aattaggctt 2888

tgattggcac ttttcgaaaa atatgcaaca attaagggat ataatctgga tggccgcttc 2948

tgtacttaat gtgaaatatt tagatacctt tcaaacactt aacagtttct ttgacaatga 3008

gttttgtaag gattggtagt aaatatcatt ccttatgacg tacattgtct gtcactaatc 3068

cttggatctt gctgtattgt cacctaaatt ggtacaggta ctgatgaaaa tctaatggat 3128

aatcataaca ctcttggtta catgtttttc ctgcagcctg aaagttttta taagaaaaag 3188

acatcaaatg cctgctgctg ccaccctttt aaattgctat cttttgaaaa gcaccagtat 3248

gtgttttaga ttgatttccc tattttaggg aaatgacagt cagtagtttc acttctgatg 3308

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aaaaaaaaaa aaaaaaaa 3386

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1               5                   10                  15

Pro Pro Pro Pro Ser Gly Ser Ser Gly Asn Glu Ala Gly Ala Gly Ala
            20                  25                  30

Ala Ala Pro Ala Ser Gln His Pro Met Thr Gly Thr Gly Ala Val Gln
        35                  40                  45

Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
    50                  55                  60

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

Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
                85                  90                  95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
            100                 105                 110

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Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
        115                 120                 125

Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
    130                 135                 140

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu
                165                 170                 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp
            180                 185                 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Ala Ala Glu
            260                 265                 270

Ala Glu Pro Glu Pro Val Glu Glu Tyr Thr Glu Gln Asn Glu Val Glu
        275                 280                 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

Ser Gly Glu Lys Glu Gln Val Asp Asp Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val
            340                 345                 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Ala Gln Asn Met Asp
385                 390                 395                 400

Ile Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415
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Gln Pro Asn Gln Val Ser Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

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

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn
        515                 520                 525

Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn
    530                 535                 540

Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560

Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

Gln Pro His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg Gly Val


        595                 600                 605

Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

Phe Ser Thr Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser
                645                 650                 655

Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn
            660                 665                 670

Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly
        675                 680                 685

Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr
    690                 695                 700
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Gln Gln Val Asn
705

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<211> 3150
<212> DNA
<213> Equus caballus

<220>
<221> CDS
<222> (1)..(1917)

<400> 17
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Met Glu Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu
1 5 10 15

agg ctt aat cag gat cag ctg gat gct gtg tct aag tac cag gaa gtc 96
Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val
20 25 30

aca aat aac ttg gag ttt gcg aaa gaa ttg cag agg agt ttc atg gcg 144
Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala
35 40 45

ttg agt cag gat att cag aaa aca ata aag aag acg gca cgt cgg gag 192
Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu
50 55 60

cag ctt atg aga gaa gaa gct gaa cag aaa cgt tta aaa act gta ctt 240
Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu
65 70 75 80

gag ctg cag tat gtt ttg gac aaa ttg gga gat gaa gaa gtg cga act 288

Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Glu Glu Val Arg Thr
85 90 95

gac ctg aaa caa ggt ttg aat gga gtg cca ata ctc tct gaa gaa gag 336
Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu
100 105 110

ttg tcg ctg ttg gat gag ttc tac aag tta gca gac cct gta cgg gac 384
Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Val Arg Asp
115 120 125

atg agc ttg agg ttg aat gag cag tat gag cat gcc tcc att cac ctg 432
Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu
130 135 140

tgg gac ttg ctg gaa ggg aag gaa aaa tct gtc tgt gga aca acc tat 480
Trp Asp Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr
145 150 155 160

aaa gct ctg agg gaa att gtt gag cgt gtt ttc cag tcc aac tac ttt 528
Lys Ala Leu Arg Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe
165 170 175

gac agc acc cac aac cac cag aat ggg ctc tgt gag gag gaa gag gct 576
Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala
180 185 190

acc tca gct cca aca gct gaa gac cag gga gct gaa gct gaa cct gag 624
Thr Ser Ala Pro Thr Ala Glu Asp Gln Gly Ala Glu Ala Glu Pro Glu
195 200 205

cca gca gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat 672
Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr

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    210                 215                 220

gta aat aga cag ttt atg gca gaa gcg cag ttc agt ggt gag aag gag        720
Val Asn Arg Gln Phe Met Ala Glu Ala Gln Phe Ser Gly Glu Lys Glu
225                 230                 235                 240

cag gtg gat gag tgg aca gtc gag acg gtc gag gtg gta aat tca ctc        768
Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu
                245                 250                 255

cag cag caa cct cag gct gca tct cct tca gta ccg gag ccc cac tct        816
Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser
            260                 265                 270

ttg act cca gtg gct cag gca gat ccc ctt gtg aga aga cag cga gta        864
Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val
        275                 280                 285

cag gac ctt atg gcg caa atg cag ggg ccc tat aat ttc ata cag gat        912
Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp
    290                 295                 300

tca atg ctg gat ttt gaa aac cag aca ctt gat cct gcc att gta tct        960
Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser
305                 310                 315                 320

gca cag cct atg aat cca gca cag aat atg gac atg ccc cag ctg gtt        1008
Ala Gln Pro Met Asn Pro Ala Gln Asn Met Asp Met Pro Gln Leu Val
                325                 330                 335

tgc cct cca gtt cat gct gaa tct aga ctt gct caa cct aat caa gtt        1056
Cys Pro Pro Val His Ala Glu Ser Arg Leu Ala Gln Pro Asn Gln Val
            340                 345                 350

cct gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt        1104
Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser
        355                 360                 365

gag ggg tat aca gca tct cag ccc ttg tac cag cct tct cat gct aca        1152
Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr
    370                 375                 380

gag caa cga ccg caa aag gaa ccg act gac cag atc cag gca aca atc        1200
Glu Gln Arg Pro Gln Lys Glu Pro Thr Asp Gln Ile Gln Ala Thr Ile
385                 390                 395                 400

tct tta aat aca gac cag act aca gca tca tca tcc ctt cct gct gct        1248
Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala
                405                 410                 415

tct cag cct cag gtg ttc cag gct ggg aca agc aaa cct tta cac agc        1296
Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser
            420                 425                 430

agt ggg atc aat gta aat gca gcg cca ttc cag tcc atg caa acg gtg        1344
Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val
        435                 440                 445

ttc aac atg aat gcc ccg gtt cct cct gtt aat gaa cca gaa act tta        1392
Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu
    450                 455                 460

aaa cag caa aat cag tac cag gcc agc tat aac cag agc ttt tcc agt        1440
Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser
465                 470                 475                 480

ccg cct cac caa gta gag cag aca gag ctt ccg caa gag cag ctt cag        1488
Pro Pro His Gln Val Glu Gln Thr Glu Leu Pro Gln Glu Gln Leu Gln
                485                 490                 495

acg gtg gtt ggt act tac cat gct tcc caa gac cag ccc cat caa gtg        1536
Thr Val Val Gly Thr Tyr His Ala Ser Gln Asp Gln Pro His Gln Val
            500                 505                 510

acc ggt aac cac cag cag cct ccc cag cag aac act ggg ttt cca cgt        1584
Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
        515                 520                 525
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        515                 520                 525

agc agt cag ccc tat tac aac agt cgt ggt gtg tct cgt gga ggc tcc       1632
Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
    530                 535                 540

cgt ggt gct aga ggc ttg atg aat gga tac agg ggc cct gcc aat gga       1680
Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
545                 550                 555                 560

ttc aga gga gga tat gat ggt tac cgc cct tcg ttc tct aac act cca       1728
Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
                565                 570                 575

aac agc ggt tac aca cag tct cag ttc agt gct ccc cgg gac tac tct       1776
Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser
            580                 585                 590

ggc tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg       1824
Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
        595                 600                 605

cag agt gga ccc cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga       1872
Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
    610                 615                 620

ccc aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa           1917
Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
625                 630                 635

tctgattcac aggattatct ttaatcgcca aaacacactg gccagtgtac cataatatgt     1977

taccagaaga gttattatct atttgttctc cctttcagga aacttattgt aaagggactg     2037

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gaagatggaa ggactggagt gtggtttggc agaacaactg catttcacag cttttcctat     2397

taaattggag cactgaatgt taaatgcata ccaaattatg catgggccct taatcacaca     2457

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taaaaggaaa agatatcaaa tgcctgctgc taccacccct ttaaattgct atcttttgaa     2937

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acactggtgt tcaacagcta gcagcttctg tggttcaccc cctgccttgt tagtgttacc     3117

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<212> PRT
<213> Equus caballus

<400> 18

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Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala
        35                  40                  45

Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu
    50                  55                  60

Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu
65                  70                  75                  80

Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Glu Glu Val Arg Thr
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Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu
            100                 105                 110

Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Val Arg Asp
        115                 120                 125

Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu
    130                 135                 140

Trp Asp Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr
145                 150                 155                 160

Lys Ala Leu Arg Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe
                165                 170                 175

Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala
            180                 185                 190

Thr Ser Ala Pro Thr Ala Glu Asp Gln Gly Ala Glu Ala Glu Pro Glu
        195                 200                 205

Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr
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Val Asn Arg Gln Phe Met Ala Glu Ala Gln Phe Ser Gly Glu Lys Glu
225                 230                 235                 240

Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu
                245                 250                 255

Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser
            260                 265                 270

Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val
```

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Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val
        275                 280                 285

Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp
    290                 295                 300

Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser
305                 310                 315                 320

Ala Gln Pro Met Asn Pro Ala Gln Asn Met Asp Met Pro Gln Leu Val
                325                 330                 335

Cys Pro Pro Val His Ala Glu Ser Arg Leu Ala Gln Pro Asn Gln Val
            340                 345                 350

Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser
        355                 360                 365

Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr
    370                 375                 380

Glu Gln Arg Pro Gln Lys Glu Pro Thr Asp Gln Ile Gln Ala Thr Ile
385                 390                 395                 400

Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala
                405                 410                 415

Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser
            420                 425                 430

Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val
        435                 440                 445

Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu
    450                 455                 460

Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser
465                 470                 475                 480

Pro Pro His Gln Val Glu Gln Thr Glu Leu Pro Gln Glu Gln Leu Gln
                485                 490                 495

Thr Val Val Gly Thr Tyr His Ala Ser Gln Asp Gln Pro His Gln Val
            500                 505                 510

Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
        515                 520                 525

Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
    530                 535                 540

Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
545                 550                 555                 560

Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
                565                 570                 575

Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser
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Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser
580 585 590

Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
595 600 605

Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
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Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
625 630 635

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<211> 6181
<212> DNA
<213> Mus musculus

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<222> (179)..(2302)

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cggggacagg gcgaagcggc ctgcgcccac ggagcgcacg tctctgttct caacgcagca 120

ccacccttgc ccccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg 178

atg ccc tcg gcc acc agc cac agc gga agc ggc agc aaa tcg tcg gga 226
Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly
1 5 10 15

ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag gcg gcg gcc ggg gca 274
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
20 25 30

gct gcg ccg gct tct cag cat ccg gca acc ggc acc ggc gcc gtc cag 322
Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
35 40 45

acc gag gcc atg aag cag att ctc ggc gta atc gac aag aaa ctt cgg 370
Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
50 55 60

aac ctg gag aag aaa aag ggt aaa ctt gat gat tac cag gaa cga atg 418
Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met
65 70 75 80

aat aaa ggg gaa agg ctc aat caa gac cag ctg gat gcc gta tct aag 466
Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
85 90 95

tac cag gaa gtc aca aat aat ttg gag ttt gca aag gaa tta cag agg 514
Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
100 105 110

agt ttc atg gca tta agt caa gat att cag aaa aca ata aag aag aca 562
Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
115 120 125

gca cgt cgg gaa cag ctt atg aga gaa gaa gca gaa cag aag cgc tta 610
Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
130 135 140

aaa act gta ctt gag tta cag tat gta ttg gat aag ctg gga gat gat 658
Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp

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145                 150                 155                 160

gat gtg aga aca gat ctg aaa caa ggt ttg agt gga gtg cca ata ttg        706
Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

tct gag gag gag ttg tca ttg ctg gat gag ttc tac aag ctc gta gat        754
Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

cct gag cgt gac atg agt tta agg tta aat gag cag tat gaa cat gcc        802
Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

tca att cac ttg tgg gat ttg ctg gaa ggg aaa gaa aag cct gtg tgt        850
Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

gga aca acc tat aaa gct cta aag gaa att gtt gag cgt gtt ttc cag        898
Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

tca aac tac ttt gat agc act cac aat cat caa aat ggg ttg tgt gag        946
Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

gag gaa gag gcg gct tca gcg ccc aca gtg gag gac cag gta gct gaa        994
Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

gct gaa cct gag cca gcg gaa gaa tac aca gag caa agt gag gtt gaa       1042
Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

tca aca gag tat gtc aat agg cag ttc atg gca gaa aca cag ttc agc       1090
Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

agt ggt gag aag gag caa gtg gat gag tgg aca gtt gaa aca gtt gag       1138
Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

gtt gta aac tca ctc cag cag caa cct cag gct gcg tcc cct tca gtc       1186
Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

cca gag ccc cac tct ttg act cca gtg gct cag tca gat cca ctt gtg       1234
Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

aga agg cag cgt gta caa gat ctt atg gca caa atg caa ggg ccc tat       1282
Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

aat ttc ata cag gat tca atg ttg gat ttt gaa aat cag acg ctt gat       1330
Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

cct gcc att gta tcc gca cag cct atg aac cct acc cag aac atg gat       1378
Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

atg cct cag ctg gtt tgc cct cag gtt cat tct gaa tct aga ctt gcc       1426
Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

caa tct aat caa gtt cct gta caa cca gaa gcc aca cag gtt cct ttg       1474
Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

gtt tca tcc aca agt gag ggg tat aca gca tct cag ccc ttg tac cag       1522
Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

cca tct cat gct acg gag cag cgg ccg cag aaa gag cca atg gat cag       1570
Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
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    450                 455                 460

att cag gca aca ata tct ttg aat aca gac cag act aca gca tcc tca       1618
Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

tcc ctt cct gct gct tct cag cct caa gtg ttc cag gct ggg aca agt       1666
Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

aaa cct ttg cac agc agt gga atc aat gta aat gca gct cca ttc cag       1714
Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

tcc atg caa acg gtg ttc aat atg aat gct cca gtc cct cct gct aat       1762
Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

gaa cca gaa acg tta aaa caa cag agt cag tac cag gcc act tat aac       1810
Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540

cag agt ttt tcc agt cag cct cac caa gtg gaa caa aca gag ctt caa       1858
Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln


545                 550                 555                 560

caa gac caa ctg caa acg gtg gtt ggc act tac cat gga tcc cag gac      1906
Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

cag cct cat caa gtg cct ggt aac cac cag caa ccc cca cag cag aac      1954
Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

act ggc ttt cca cgt agc agt cag cct tat tac aac agt cgt ggg gta      2002
Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605

tct cga gga ggg tct cgt ggt gcc aga ggc ttg atg aat gga tac agg      2050
Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

ggc cct gcc aat gga ttt aga gga gga tat gat ggt tac cgc cct tca      2098
Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

ttc tcg aac act cca aac agt ggt tat tca cag tct cag ttc act gct      2146
Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
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ccc cgg gac tac tct ggt tac cag cgg gat gga tat cag cag aat ttc      2194
Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

aag cga ggc tct ggg cag agt gga cca cgg gga gcc cca cga ggt cgt      2242
Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg
        675                 680                 685

gga ggg ccc cca aga ccc aac aga ggg atg ccg caa atg aac act cag      2290
Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln
    690                 695                 700

caa gtg aat taa tgtgatacac aggattatgt ttaatcgcca aaaacacact          2342
Gln Val Asn
705

ggccagtgta ccataatatg ttaccagaag agttattatc tatttgttct ccctttcagg    2402

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<211> 707
<212> PRT
<213> Mus musculus

<400> 20

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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
            20                  25                  30


Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
        35                  40                  45


Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
    50                  55                  60


Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met
65                  70                  75                  80
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Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
                85                  90                  95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
            100                 105                 110

Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
        115                 120                 125

Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
    130                 135                 140

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380
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Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

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

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540

Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln

545                 550                 555                 560

Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605

Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655

Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg
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        675                 680                 685

Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln
    690                 695                 700

Gln Val Asn
705
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<222> (139)..(2262)

<400> 21

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tctcttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc       171
                    Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly
                    1               5                   10

agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag       219

Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu
            15                  20                  25

gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc     267
Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly
        30                 35                  40

acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc     315
Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile
    45                  50                 55

gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat     363
Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
60                  65                 70                  75

tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg     411
Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
                80                 85                  90

gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca     459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
            95                 100                 105

aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa     507
Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
        110                115                 120

aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca     555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
    125                 130                135

gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat     603
Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
140                 145                150                 155

aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt     651
Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
                160                165                 170
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gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc      699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
            175                 180                 185

tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag      747
Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu
        190                 195                 200

cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa      795
Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys
    205                 210                 215

gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt      843
Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val
220                 225                 230                 235

gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa      891
Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln
            240                 245                 250

aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag      939
Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu
            255                 260                 265

gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag      987
Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu
        270                 275                 280

caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca      1035
Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala
    285                 290                 295

gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca      1083
Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr
300                 305                 310                 315

gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct      1131
Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala
            320                 325                 330

gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag      1179
Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln
            335                 340                 345

tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa      1227
Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln
        350                 355                 360

atg caa ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt gaa      1275
Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu
    365                 370                 375

aat cag acg ctt gat cct gcc att gta tcc gca cag cct atg aac cct      1323
Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro
380                 385                 390                 395

acc cag aac atg gat atg cct cag ctg gtt tgc cct cag gtt cat tct      1371
Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val His Ser
            400                 405                 410

gaa tct aga ctt gcc caa tct aat caa gtt cct gta caa cca gaa gcc      1419
Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala
            415                 420                 425

aca cag gtt cct ttg gtt tca tcc aca agt gag ggg tat aca gca tct      1467
Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser
        430                 435                 440

cag ccc ttg tac cag cca tct cat gct acg gag cag cgg ccg cag aaa      1515
Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys
    445                 450                 455

gag cca atg gat cag att cag gca aca ata tct ttg aat aca gac cag      1563
Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln
460                 465                 470                 475
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act aca gca tcc tca tcc ctt cct gct gct tct cag cct caa gtg ttc      1611
Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe
                480                 485                 490

cag gct ggg aca agt aaa cct ttg cac agc agt gga atc aat gta aat      1659
Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn
            495                 500                 505

gca gct cca ttc cag tcc atg caa acg gtg ttc aat atg aat gct cca      1707
Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro
        510                 515                 520

gtc cct cct gct aat gaa cca gaa acg tta aaa caa cag agt cag tac        1755
Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr
    525                 530                 535

cag gcc act tat aac cag agt ttt tcc agt cag cct cac caa gtg gaa        1803
Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu
540                 545                 550                 555

caa aca gag ctt caa caa gac caa ctg caa acg gtg gtt ggc act tac        1851
Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr
                560                 565                 570

cat gga tcc cag gac cag cct cat caa gtg cct ggt aac cac cag caa        1899
His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln
            575                 580                 585

ccc cca cag cag aac act ggc ttt cca cgt agc agt cag cct tat tac        1947
Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr
        590                 595                 600

aac agt cgt ggg gta tct cga gga ggg tct cgt ggt gcc aga ggc ttg        1995
Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu
    605                 610                 615

atg aat gga tac agg ggc cct gcc aat gga ttt aga gga gga tat gat        2043
Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp
620                 625                 630                 635

ggt tac cgc cct tca ttc tcg aac act cca aac agt ggt tat tca cag        2091
Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln
                640                 645                 650

tct cag ttc act gct ccc cgg gac tac tct ggt tac cag cgg gat gga        2139
Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly
            655                 660                 665

tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga        2187
Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly
        670                 675                 680

gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg        2235
Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro
    685                 690                 695

caa atg aac act cag caa gtg aat taa tgtgatacac aggattatgt              2282
Gln Met Asn Thr Gln Gln Val Asn
700                 705

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Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
        35                  40                  45

Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
    50                  55                  60

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

Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
                85                  90                  95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
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Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
                100                 105                 110

Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
        115                 120                 125

Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
    130                 135                 140

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu


            260                 265                 270

Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400
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Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

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

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540

Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560

Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605

Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655

Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg
        675                 680                 685
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Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln
    690                 695                 700


Gln Val Asn
705
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<222> (139)..(2235)

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tctcttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc      171
                    Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly
                    1               5                   10

agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag      219
Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu
            15                  20                  25

gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc      267
Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly
        30                  35                  40

acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc      315
Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile
    45                  50                  55

gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat      363
Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
60                  65                  70                  75

tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg      411
Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
                80                  85                  90

gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca      459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
            95                  100                 105

aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa      507
Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
        110                 115                 120

aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca      555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
    125                 130                 135

gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat      603
Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
140                 145                 150                 155

aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt      651
Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
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gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc      699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
            175                 180                 185

tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag      747
Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu
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cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa       795
Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys
    205                 210                 215

gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt       843
Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val
220                 225                 230                 235

gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa       891
Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln
                240                 245                 250

aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag       939
Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu
            255                 260                 265

gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag       987
Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu
        270                 275                 280

caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca       1035
Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala
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gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca       1083
Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr
300                 305                 310                 315

gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct       1131
Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala
                320                 325                 330

gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag       1179
Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln
            335                 340                 345

tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa       1227
Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln
        350                 355                 360

atg caa ggg ccc tat aat ttc ata cag acg ctt gat cct gcc att gta       1275
Met Gln Gly Pro Tyr Asn Phe Ile Gln Thr Leu Asp Pro Ala Ile Val
    365                 370                 375

tcc gca cag cct atg aac cct acc cag aac atg gat atg cct cag ctg       1323
Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu
380                 385                 390                 395

gtt tgc cct cag gtt cat tct gaa tct aga ctt gcc caa tct aat caa       1371
Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala Gln Ser Asn Gln
                400                 405                 410

gtt cct gta caa cca gaa gcc aca cag gtt cct ttg gtt tca tcc aca       1419
Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr
            415                 420                 425

agt gag ggg tat aca gca tct cag ccc ttg tac cag cca tct cat gct       1467
Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala
        430                 435                 440

acg gag cag cgg ccg cag aaa gag cca atg gat cag att cag gca aca       1515
Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln Ile Gln Ala Thr
    445                 450                 455

ata tct ttg aat aca gac cag act aca gca tcc tca tcc ctt cct gct       1563
Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala
460                 465                 470                 475

gct tct cag cct caa gtg ttc cag gct ggg aca agt aaa cct ttg cac       1611
Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His


                480                 485                 490
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agc agt gga atc aat gta aat gca gct cca ttc cag tcc atg caa acg      1659
Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr
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gtg ttc aat atg aat gct cca gtc cct cct gct aat gaa cca gaa acg      1707
Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn Glu Pro Glu Thr
        510                 515                 520

tta aaa caa cag agt cag tac cag gcc act tat aac cag agt ttt tcc      1755
Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn Gln Ser Phe Ser
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agt cag cct cac caa gtg gaa caa aca gag ctt caa caa gac caa ctg      1803
Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln Gln Asp Gln Leu
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caa acg gtg gtt ggc act tac cat gga tcc cag gac cag cct cat caa      1851
Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln
                560                 565                 570

gtg cct ggt aac cac cag caa ccc cca cag cag aac act ggc ttt cca      1899
Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro
            575                 580                 585

cgt agc agt cag cct tat tac aac agt cgt ggg gta tct cga gga ggg      1947
Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly
        590                 595                 600

tct cgt ggt gcc aga ggc ttg atg aat gga tac agg ggc cct gcc aat      1995
Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn
    605                 610                 615

gga ttt aga gga gga tat gat ggt tac cgc cct tca ttc tcg aac act      2043
Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr
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cca aac agt ggt tat tca cag tct cag ttc act gct ccc cgg gac tac      2091
Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala Pro Arg Asp Tyr
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tct ggt tac cag cgg gat gga tat cag cag aat ttc aag cga ggc tct      2139
Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser
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ggg cag agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca      2187
Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro
        670                 675                 680

aga ccc aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa      2235
Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
    685                 690                 695

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gaaactattt ttattctgca tgttctgtcc taagcgtcat cttgagcctt gcacacaata    2475

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35 40 45

Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
50 55 60

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

Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
85 90 95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
100 105 110

Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
115 120 125

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Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
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Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

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

Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val
385                 390                 395                 400

His Ser Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro
                405                 410                 415

Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr
            420                 425                 430
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Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro
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Gln Lys Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr
    450                 455                 460

Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln
465                 470                 475                 480

Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn
                485                 490                 495

Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn
            500                 505                 510

Ala Pro Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser
        515                 520                 525

Gln Tyr Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln
    530                 535                 540

Val Glu Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly
545                 550                 555                 560

Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His
                565                 570                 575

Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro
            580                 585                 590

Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg
        595                 600                 605

Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly
    610                 615                 620

Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr
625                 630                 635                 640

Ser Gln Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg
                645                 650                 655

Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro
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ccacccttgc cccccteggc tgcccactcc agacgtccag cggctccgcg cgcgcacg        178

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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly
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ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag gcg gcg gcc ggg gca        274
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
            20                  25                  30

gct gcg ccg gct tct cag cat ccg gca acc ggc acc ggc gcc gtc cag        322
Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
        35                  40                  45

acc gag gcc atg aag cag att ctc ggc gta atc gac aag aaa ctt cgg        370
Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
    50                  55                  60

aac ctg gag aag aaa aag ggt aaa ctt gat gat tac cag gaa cga atg        418
Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met
65                  70                  75                  80

aat aaa ggg gaa agg ctc aat caa gac cag ctg gat gcc gta tct aag        466
Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
                85                  90                  95

tac cag gaa gtc aca aat aat ttg gag ttt gca aag gaa tta cag agg        514
Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
            100                 105                 110

agt ttc atg gca tta agt caa gat att cag aaa aca ata aag aag aca        562
Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
        115                 120                 125

gca cgt cgg gaa cag ctt atg aga gaa gaa gca gaa cag aag cgc tta        610
Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
    130                 135                 140

aaa act gta ctt gag tta cag tat gta ttg gat aag ctg gga gat gat        658
Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

gat gtg aga aca gat ctg aaa caa ggt ttg agt gga gtg cca ata ttg        706
Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

tct gag gag gag ttg tca ttg ctg gat gag ttc tac aag ctc gta gat        754
Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

cct gag cgt gac atg agt tta agg tta aat gag cag tat gaa cat gcc        802
Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
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tca att cac ttg tgg gat ttg ctg gaa ggg aaa gaa aag cct gtg tgt        850
Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

gga aca acc tat aaa gct cta aag gaa att gtt gag cgt gtt ttc cag        898
Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240
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tca aac tac ttt gat agc act cac aat cat caa aat ggg ttg tgt gag         946
Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

gag gaa gag gcg gct tca gcg ccc aca gtg gag gac cag gta gct gaa         994
Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

gct gaa cct gag cca gcg gaa gaa tac aca gag caa agt gag gtt gaa        1042
Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

tca aca gag tat gtc aat agg cag ttc atg gca gaa aca cag ttc agc        1090
Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

agt ggt gag aag gag caa gtg gat gag tgg aca gtt gaa aca gtt gag        1138
Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

gtt gta aac tca ctc cag cag caa cct cag gct gcg tcc cct tca gtc        1186
Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

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Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

aga agg cag cgt gta caa gat ctt atg gca caa atg caa ggg ccc tat        1282
Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

aat ttc ata cag gat tca atg ttg gat ttt gaa aat cag acg ctt gat        1330
Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

cct gcc att gta tcc gca cag cct atg aac cct acc cag aac atg gat        1378
Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

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Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
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caa tct aat caa gtt cct gta caa cca gaa gcc aca cag gtt cct ttg        1474
Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

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Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
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Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
    450                 455                 460

att cag gca aca ata tct ttg aat aca gac cag act aca gca tcc tca        1618
Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

tcc ctt cct gct gct tct cag cct caa gtg ttc cag gct ggg aca agt        1666
Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

aaa cct ttg cac agc agt gga atc aat gta aat gca gct cca ttc cag        1714
Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

tcc atg caa acg gtg ttc aat atg aat gct cca gtc cct cct gct aat        1762
Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

gaa cca gaa acg tta aaa caa cag agt cag tac cag gcc act tat aac        1810
Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540
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cag agt ttt tcc agt cag cct cac caa gtg gaa caa aca gag ctt caa      1858
Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560

caa gac caa ctg caa acg gtg gtt ggc act tac cat gga tcc cag gac      1906
Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

cag cct cat caa gtg cct ggt aac cac cag caa ccc cca cag cag aac      1954
Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

act ggc ttt cca cgt agc agt cag cct tat tac aac agt cgt ggg gta      2002
Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605

tct cga gga ggg tct cgt ggt gcc aga ggc ttg atg aat gga tac agg      2050
Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

ggc cct gcc aat gga ttt aga gga gga tat gat ggt tac cgc cct tca      2098
Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

ttc tcg aac act cca aac agt ggt tat tca cag tct cag ttc act gct      2146
Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655

ccc cgg gac tac tct ggt tac cag cgg gat gga tat cag cag aat ttc      2194
Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

aag cga ggc tct ggg cag agt gga cca cgg gga gcc cca cga ggt aat      2242
Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn
        675                 680                 685

ata ttg tgg tgg tga tcctagctcc tatgtggagc ttctgttctg gccttggaag      2297
Ile Leu Trp Trp
    690

aactgttcat agtccgcatg taggttacat gttaggaata catttatctt ttccagactt    2357

gttgctaaag attaaatgaa atgctctgtt tctaaaattt catcttgaat ccaaatttta    2417

atttttgaat gactttccct gctgttgtct tcaaaatcag aacattttct ctgcctcaga    2477

aaagcgtttt tccaactgga aatttatttt tcaggtctta aaacctgcta aatgttttta    2537

ggaagtacct actgaaactt tttgtaagac atttttggaa cgagcttgaa catttatata    2597

aatttattac cctctttgat ttttgaaaca tgcatattat atttaggctg agaagccctt    2657

caaatggcca gataagccac agttttagct agagaaccat ttagaattga cataactaat    2717

ctaaacttga acacttttag gaccaatgtt agtgttctaa ataccaacat atttctgatg    2777

tttaaacaga tctcccaaat tcttaggacc ttgatgtcat taaaatttag aatgacaagc    2837

ttaagaggct ttagtttcat ttgtttttca agtaatgaaa aataatttct tacatgggca    2897

gatagttaat ttgttgaaca attacaggta gcatttcatg taatctgatg ttctaaatgg    2957

ttctcttatt gaaggaggtt aaagaattag gtttcttaca gtttttggct ggccatgaca    3017

tgtataaaat gtatattaag gaggaattat aaagtacttt aatttgaatg ctagtggcaa    3077

ttgatcatta agaaagtact ttaaagcaaa aggttaatgg gtcatctggg aaaaatactg    3137

aagtatcaaa ggtatttgca tgtgaatgtg ggttatgttc ttctatccca ccttgtagca    3197

tattctatga aagttgagtt aaatgatagc taaaatatct gtttcaacag catgtaaaaa    3257

gttattttaa ctgttacaag tcattataca attttgaatg ttctgtagtt tctttttaac    3317
```

```
agtttaggta caaaggtctg ttttcattct ggtgcttttt attaattttg atagtatgat      3377

gtcacttcct attgaaatgt aagctagcgt gtaccttaga atgtgagctc catgagagca      3437

ggtaccttgt ttgtcttcac tgctgtatct attcccaacg cctcatgaca gtgcctggca      3497

catagtaggc actcaataaa tacttgttga atgaatgaaa aaaaaaaaaa a               3548
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<210> 26
<211> 692
<212> PRT
<213> Mus musculus

<400> 26

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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly
1               5                   10                  15

Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
            20                  25                  30

Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
        35                  40                  45

Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
    50                  55                  60

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

Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
                85                  90                  95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
            100                 105                 110

Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
        115                 120                 125

Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
    130                 135                 140

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
```

```
225                 230                 235                 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

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

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
```

```
    530                 535                 540


Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560


Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575


Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn


            580                 585                 590


Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605


Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620


Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640


Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655


Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670


Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn
        675                 680                 685


Ile Leu Trp Trp
    690
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<210> 27
<211> 3508
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (139)..(2217)

<400> 27

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cccaccgcgc gcgcgcgtag ccgcctgccc gcccgcccgc tgcgcgtttt gtcccgcgtc       60

tctccccgtc cgtctcctga cttgctggtc ttgtccttcc ctcccgcttt tttcctctcc      120

tctcttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc        171
                    Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly
                    1               5                   10

agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag        219
Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu
            15                  20                  25

gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc        267
Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly
```

```
        30                  35                  40

acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc       315
Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile
    45                  50                  55

gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat       363

Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
60                  65                  70                  75

tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg       411
Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
                80                  85                  90

gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca       459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
            95                  100                 105

aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa       507
Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
        110                 115                 120

aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca       555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
    125                 130                 135

gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat       603
Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
140                 145                 150                 155

aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt       651
Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
                160                 165                 170

gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc       699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
            175                 180                 185

tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag       747
Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu
        190                 195                 200

cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa       795
Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys
    205                 210                 215

gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt       843
Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val
220                 225                 230                 235

gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa       891
Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln
                240                 245                 250

aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag       939
Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu
            255                 260                 265

gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag       987
Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu
        270                 275                 280

caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca      1035
Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala
    285                 290                 295

gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca      1083
Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr
300                 305                 310                 315

gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct     1131
Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala
                320                 325                 330
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gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag      1179
Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln
            335                 340                 345

tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa      1227
Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln
        350                 355                 360

atg caa ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt gaa      1275
Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu
    365                 370                 375

aat cag acg ctt gat cct gcc att gta tcc gca cag cct atg aac cct      1323
Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro
380                 385                 390                 395

acc cag aac atg gat atg cct cag ctg gtt tgc cct cag gtt cat tct      1371
Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val His Ser
                400                 405                 410

gaa tct aga ctt gcc caa tct aat caa gtt cct gta caa cca gaa gcc      1419
Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala
            415                 420                 425

aca cag gtt cct ttg gtt tca tcc aca agt gag ggg tat aca gca tct      1467
Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser
        430                 435                 440

cag ccc ttg tac cag cca tct cat gct acg gag cag cgg ccg cag aaa      1515
Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys
    445                 450                 455

gag cca atg gat cag att cag gca aca ata tct ttg aat aca gac cag      1563
Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln
460                 465                 470                 475

act aca gca tcc tca tcc ctt cct gct gct tct cag cct caa gtg ttc      1611
Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe
                480                 485                 490

cag gct ggg aca agt aaa cct ttg cac agc agt gga atc aat gta aat      1659
Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn
            495                 500                 505

gca gct cca ttc cag tcc atg caa acg gtg ttc aat atg aat gct cca      1707
Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro
        510                 515                 520

gtc cct cct gct aat gaa cca gaa acg tta aaa caa cag agt cag tac      1755
Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr
    525                 530                 535

cag gcc act tat aac cag agt ttt tcc agt cag cct cac caa gtg gaa      1803
Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu
540                 545                 550                 555

caa aca gag ctt caa caa gac caa ctg caa acg gtg gtt ggc act tac      1851
Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr
                560                 565                 570

cat gga tcc cag gac cag cct cat caa gtg cct ggt aac cac cag caa      1899
His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln
            575                 580                 585

ccc cca cag cag aac act ggc ttt cca cgt agc agt cag cct tat tac      1947
Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr
        590                 595                 600

aac agt cgt ggg gta tct cga gga ggg tct cgt ggt gcc aga ggc ttg      1995
Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu
    605                 610                 615

atg aat gga tac agg ggc cct gcc aat gga ttt aga gga gga tat gat      2043
Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp
620                 625                 630                 635
```

```
ggt tac cgc cct tca ttc tcg aac act cca aac agt ggt tat tca cag        2091
Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln
                640                 645                 650

tct cag ttc act gct ccc cgg gac tac tct ggt tac cag cgg gat gga        2139
Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly
            655                 660                 665

tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga        2187
Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly
        670                 675                 680

gcc cca cga ggt aat ata ttg tgg tgg tga tcctagctcc tatgtggagc          2237
Ala Pro Arg Gly Asn Ile Leu Trp Trp
    685                 690

ttctgttctg gccttggaag aactgttcat agtccgcatg taggttacat gttaggaata      2297

catttatctt ttccagactt gttgctaaag attaaatgaa atgctctgtt tctaaaattt      2357

catcttgaat ccaaatttta atttttgaat gactttccct gctgttgtct tcaaaatcag      2417

aacattttct ctgcctcaga aaagcgtttt tccaactgga aatttatttt tcaggtctta      2477

aaacctgcta aatgttttta ggaagtacct actgaaactt tttgtaagac atttttggaa      2537

cgagcttgaa catttatata aatttattac cctctttgat ttttgaaaca tgcatattat      2597

atttaggctg agaagccctt caaatggcca gataagccac agttttagct agagaaccat      2657

ttagaattga cataactaat ctaaacttga acacttttag gaccaatgtt agtgttctaa      2717

ataccaacat atttctgatg tttaaacaga tctcccaaat tcttaggacc ttgatgtcat      2777

taaaatttag aatgacaagc ttaagaggct ttagtttcat ttgtttttca agtaatgaaa      2837

aataatttct tacatgggca gatagttaat ttgttgaaca attacaggta gcatttcatg      2897

taatctgatg ttctaaatgg ttctcttatt gaaggaggtt aaagaattag gtttcttaca      2957

gtttttggct ggccatgaca tgtataaaat gtatattaag gaggaattat aaagtacttt      3017

aatttgaatg ctagtggcaa ttgatcatta agaaagtact ttaaagcaaa aggttaatgg      3077

gtcatctggg aaaaatactg aagtatcaaa ggtatttgca tgtgaatgtg ggttatgttc      3137

ttctatccca ccttgtagca tattctatga aagttgagtt aaatgatagc taaaatatct      3197

gtttcaacag catgtaaaaa gttattttaa ctgttacaag tcattataca attttgaatg      3257

ttctgtagtt tctttttaac agtttaggta caaaggtctg ttttcattct ggtgcttttt      3317

attaattttg atagtatgat gtcacttcct attgaaatgt aagctagcgt gtaccttaga      3377

atgtgagctc catgagagca ggtaccttgt ttgtcttcac tgctgtatct attcccaacg      3437

cctcatgaca gtgcctggca catagtaggc actcaataaa tacttgttga atgaatgaaa      3497

aaaaaaaaaa a                                                           3508
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<210> 28

<211> 692

<212> PRT

<213> Mus musculus

<400> 28

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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly
1               5                   10                  15
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```
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
            20                  25                  30

Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
        35                  40                  45

Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
    50                  55                  60

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

Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
                85                  90                  95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
            100                 105                 110

Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
        115                 120                 125

Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu
    130                 135                 140

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145                 150                 155                 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu


                165                 170                 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300
```

```
Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

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

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540

Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560

Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605
```

```
Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655

Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn
        675                 680                 685

Ile Leu Trp Trp
    690
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<210> 29

<211> 2109

<212> DNA

<213> Gallus gallus

<220>

<221> CDS

<222> (1)..(2109)

<400> 29

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atg ccc tcg gct acc aac ggc acc atg gcg agc agc agc ggg aag gcg       48
Met Pro Ser Ala Thr Asn Gly Thr Met Ala Ser Ser Ser Gly Lys Ala
1               5                   10                  15

ggc ccg ggc ggc aac gag cag gcc ccg gcg gcg gca gcg gcg gcc ccg       96
Gly Pro Gly Gly Asn Glu Gln Ala Pro Ala Ala Ala Ala Ala Ala Pro
            20                  25                  30

cag gcg tcg ggc ggc agc atc acc tcg gtt cag acc gag gcc atg aag      144
Gln Ala Ser Gly Gly Ser Ile Thr Ser Val Gln Thr Glu Ala Met Lys
        35                  40                  45

cag atc ttg gga gtg atc gac aaa aag ctc cgc aac ctc gag aag aaa      192
Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys
    50                  55                  60

aag agc aaa ctt gac gat tac cag gaa cga atg aac aag ggg gaa cgt      240
Lys Ser Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
65                  70                  75                  80

cta aat caa gat caa ctg gat gca gtg tca aaa tac cag gaa gtg aca      288
Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
                85                  90                  95

aat aac ctg gaa ttc gct aaa gaa ctg cag agg agc ttt atg gca ctg      336
Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
            100                 105                 110

agc caa gat atc cag aaa aca ata aaa aag acg gct cgc agg gag cag      384
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
        115                 120                 125

ctg atg aga gaa gag gct gag cag aag cgt tta aag act gtg cta gag      432
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
    130                 135                 140
```

```
ctg cag ttc att ttg gac aag ttg ggt gac gat gaa gtg cgc agt gac       480
Leu Gln Phe Ile Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Ser Asp
145                 150                 155                 160

ttg aaa caa gga tca aat gga gta ccg gta ctg aca gag gag gaa ctg       528
Leu Lys Gln Gly Ser Asn Gly Val Pro Val Leu Thr Glu Glu Glu Leu
                165                 170                 175

aca atg ctg gat gaa ttt tac aag cta gtt tac cct gaa agg gac atg       576
Thr Met Leu Asp Glu Phe Tyr Lys Leu Val Tyr Pro Glu Arg Asp Met
            180                 185                 190

aac atg agg ttg aat gag cag tat gag caa gca tct gtt cac ctg tgg       624
Asn Met Arg Leu Asn Glu Gln Tyr Glu Gln Ala Ser Val His Leu Trp
        195                 200                 205

gac tta ctg gaa ggg aag gaa aaa ccc gtt tgt gga aca acc tat aaa       672
Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
    210                 215                 220

gcc ctg aag gag gtt gtt gaa cgt att ctt caa act agt tac ttt gat       720
Ala Leu Lys Glu Val Val Glu Arg Ile Leu Gln Thr Ser Tyr Phe Asp
225                 230                 235                 240

agc acc cat aac cat cag aac ggg tta tgt gag gaa gaa gag gca gca       768
Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala
                245                 250                 255

ccc aca cct gca gta gaa gac act gta gca gaa gct gag cct gat cca       816
Pro Thr Pro Ala Val Glu Asp Thr Val Ala Glu Ala Glu Pro Asp Pro
            260                 265                 270

gca gaa gaa ttt act gaa cct act gaa gtt gaa tcg act gag tat gta       864
Ala Glu Glu Phe Thr Glu Pro Thr Glu Val Glu Ser Thr Glu Tyr Val
        275                 280                 285

aac aga caa ttc atg gca gag act cag ttc agc agt agt gag aag gaa       912
Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Ser Glu Lys Glu
    290                 295                 300

cag gta gat gag tgg aca gtt gaa acg gtt gag gtt gta aat tca ctg       960
Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu
305                 310                 315                 320

cag caa caa aca caa gct aca tct cct cca gtt cct gaa cct cat aca      1008
Gln Gln Gln Thr Gln Ala Thr Ser Pro Pro Val Pro Glu Pro His Thr
                325                 330                 335

ctc act act gtg gct caa gca gat cct ctt gtt aga aga cag aga gta      1056
Leu Thr Thr Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val
            340                 345                 350

cag gac ctt atg gcc cag atg cag ggt cca tat aac ttc atg cag gac      1104
Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Met Gln Asp
        355                 360                 365

tct atg ctg gag ttt gag aac cag aca ctt gat cct gcc att gta tct      1152
Ser Met Leu Glu Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser
    370                 375                 380

gca cag ccc atg aat cca gca cag aat ttg gac atg ccg caa atg gtc      1200
Ala Gln Pro Met Asn Pro Ala Gln Asn Leu Asp Met Pro Gln Met Val
385                 390                 395                 400

tgc cct cca gtt cat act gag tca aga ctt gcc cag cct aat caa gtt      1248
Cys Pro Pro Val His Thr Glu Ser Arg Leu Ala Gln Pro Asn Gln Val
                405                 410                 415

cct gtg caa cca gaa gct acg cag gtt ccc ttg gtt tca tct aca agt      1296
Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser

            420                 425                 430

gag gga tat aca gcc tcc cag ccc atg tat cag cct tct cat acc aca      1344
Glu Gly Tyr Thr Ala Ser Gln Pro Met Tyr Gln Pro Ser His Thr Thr
```

```
        435                 440                 445

gag caa cgg cca cag aag gaa tcc att gac cag att cag gct tca atg     1392
Glu Gln Arg Pro Gln Lys Glu Ser Ile Asp Gln Ile Gln Ala Ser Met
    450                 455                 460

tca ctg aat gca gac cag acc ccg tca tca tca tca ctt ccc act gca     1440
Ser Leu Asn Ala Asp Gln Thr Pro Ser Ser Ser Ser Leu Pro Thr Ala
465                 470                 475                 480

tcc cag ccg caa gtt ttc caa gct gga tct agc aaa cct ttg cat agc     1488
Ser Gln Pro Gln Val Phe Gln Ala Gly Ser Ser Lys Pro Leu His Ser
                485                 490                 495

agc gga atc aat gtt aat gca gct cca ttc caa tcc atg caa aca gta     1536
Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val
            500                 505                 510

ttc aac atg aat gca cct gtt cct cct gtt aat gag cca gaa gcc ctt     1584
Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Ala Leu
        515                 520                 525

aag caa caa aat cag tac cag gcc agt tac aac cag agt ttc tcc aat     1632
Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Asn
    530                 535                 540

cag cca cac caa gta gaa caa tca gat ctt cag caa gaa cag ctc cag     1680
Gln Pro His Gln Val Glu Gln Ser Asp Leu Gln Gln Glu Gln Leu Gln
545                 550                 555                 560

aca gtg gtt ggt act tac cat ggt tct ccg gac cag acc cat caa gtg     1728
Thr Val Val Gly Thr Tyr His Gly Ser Pro Asp Gln Thr His Gln Val
                565                 570                 575

gca gga aac cac cag caa cct ccc cag cag aat act gga ttt cca cgc     1776
Ala Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
            580                 585                 590

aac agt cag cct tat tac aac agt cgg gga gtg tct cgt ggt gga tca     1824
Asn Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
        595                 600                 605

cgt ggg act cgt gga ttg atg aat ggt tac agg gga cct gca aat gga     1872
Arg Gly Thr Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
    610                 615                 620

ttt aga gga gga tat gat ggc tac cgt cct tca ttt tcc aac act ccg     1920
Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
625                 630                 635                 640

aac agt ggt tac acg cag ccc caa ttt aat gct cct cga gat tat tca     1968
Asn Ser Gly Tyr Thr Gln Pro Gln Phe Asn Ala Pro Arg Asp Tyr Ser
                645                 650                 655

aac tac cag cgg gat gga tat cag cag aac ttc aaa cgt ggt tct gga     2016
Asn Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
            660                 665                 670

caa agt ggg cct cgg gga gct cct cga ggt cgt gga ggg ccc cca aga     2064

Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
        675                 680                 685

cca aac aga ggg atg cct caa atg aac gct cag caa gtg aat taa            2109
Pro Asn Arg Gly Met Pro Gln Met Asn Ala Gln Gln Val Asn
    690                 695                 700
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<210> 30

<211> 702

<212> PRT

<213> Gallus gallus

<400> 30

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Met Pro Ser Ala Thr Asn Gly Thr Met Ala Ser Ser Ser Gly Lys Ala
1               5                   10                  15

Gly Pro Gly Gly Asn Glu Gln Ala Pro Ala Ala Ala Ala Ala Ala Pro
            20                  25                  30

Gln Ala Ser Gly Gly Ser Ile Thr Ser Val Gln Thr Glu Ala Met Lys
        35                  40                  45

Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys
    50                  55                  60

Lys Ser Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
65                  70                  75                  80

Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
                85                  90                  95

Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
            100                 105                 110

Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
        115                 120                 125

Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
    130                 135                 140

Leu Gln Phe Ile Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Ser Asp
145                 150                 155                 160

Leu Lys Gln Gly Ser Asn Gly Val Pro Val Leu Thr Glu Glu Glu Leu
                165                 170                 175

Thr Met Leu Asp Glu Phe Tyr Lys Leu Val Tyr Pro Glu Arg Asp Met
            180                 185                 190

Asn Met Arg Leu Asn Glu Gln Tyr Glu Gln Ala Ser Val His Leu Trp
        195                 200                 205

Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
    210                 215                 220

Ala Leu Lys Glu Val Val Glu Arg Ile Leu Gln Thr Ser Tyr Phe Asp
225                 230                 235                 240

Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala
                245                 250                 255

Pro Thr Pro Ala Val Glu Asp Thr Val Ala Glu Ala Glu Pro Asp Pro
            260                 265                 270

Ala Glu Glu Phe Thr Glu Pro Thr Glu Val Glu Ser Thr Glu Tyr Val
        275                 280                 285

Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Ser Glu Lys Glu
    290                 295                 300
```

```
    290                 295                 300

Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu
305                 310                 315                 320

Gln Gln Gln Thr Gln Ala Thr Ser Pro Pro Val Pro Glu Pro His Thr
                325                 330                 335

Leu Thr Thr Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val
            340                 345                 350

Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Met Gln Asp
        355                 360                 365

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

Ala Gln Pro Met Asn Pro Ala Gln Asn Leu Asp Met Pro Gln Met Val
385                 390                 395                 400

Cys Pro Pro Val His Thr Glu Ser Arg Leu Ala Gln Pro Asn Gln Val
                405                 410                 415

Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser
            420                 425                 430

Glu Gly Tyr Thr Ala Ser Gln Pro Met Tyr Gln Pro Ser His Thr Thr
        435                 440                 445

Glu Gln Arg Pro Gln Lys Glu Ser Ile Asp Gln Ile Gln Ala Ser Met
    450                 455                 460

Ser Leu Asn Ala Asp Gln Thr Pro Ser Ser Ser Ser Leu Pro Thr Ala
465                 470                 475                 480

Ser Gln Pro Gln Val Phe Gln Ala Gly Ser Ser Lys Pro Leu His Ser
                485                 490                 495

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

Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Ala Leu
        515                 520                 525

Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Asn
    530                 535                 540

Gln Pro His Gln Val Glu Gln Ser Asp Leu Gln Gln Glu Gln Leu Gln
545                 550                 555                 560

Thr Val Val Gly Thr Tyr His Gly Ser Pro Asp Gln Thr His Gln Val
                565                 570                 575

Ala Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
            580                 585                 590

Asn Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
        595                 600                 605
```

```
Arg Gly Thr Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
    610                 615                 620

Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
625                 630                 635                 640

Asn Ser Gly Tyr Thr Gln Pro Gln Phe Asn Ala Pro Arg Asp Tyr Ser
                645                 650                 655

Asn Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
            660                 665                 670

Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
        675                 680                 685

Pro Asn Arg Gly Met Pro Gln Met Asn Ala Gln Gln Val Asn
    690                 695                 700
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<210> 31
<211> 20
<212> DNA
<213> Artificial

<220>
<223> T3 primer

<400> 31
aattaaccct cactaaaggg 20

<210> 32
<211> 19
<212> DNA
<213> Artificial

<220>
<223> T7 primer

<400> 32
taatacgact cactatagg 19

<210> 33
<211> 18
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 33
aaggtttgaa tggagtgc 18

<210> 34
<211> 18
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 34
tgctcctttt caccactg 18

<210> 35
<211> 18
<212> DNA
<213> Artificial

<220>
<223> GAPDH primer

<400> 35
gggctgcttt taactctg 18

<210> 36
<211> 18
<212> DNA
<213> Artificial

<220>
<223> GAPDH primer

<400> 36
ccaggaaatg agcttgac 18

<210> 37
<211> 14
<212> PRT
<213> Artificial

<220>
<223> peptides

<400> 37
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Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln
1               5                   10
```

<210> 38
<211> 22
<212> DNA

<213> Artificial

<220>
<223> primer

<400> 38
aggtsharct gcagsagtcw gg 22

<210> 39
<211> 23
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 39
ctcgagttaa ttcacttgct gag 23

<210> 40
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> primer

<400> 40
ggtaccattc acttgctgag tg 22

<210> 41
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> primer

<400> 41
gagctcatgc cctcggccac cag 23

<210> 42
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> primer

<400> 42
ctcgagttaa ttcacttgct gag          23

<210> 43
<211> 14
<212> PRT
<213> Homo sapiens

<400> 43

```
Arg Asn Leu Gln Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln
1               5                   10
```

<210> 44
<211> 148
<212> PRT
<213> Mus musculus

<400> 44

```
Met Glu Trp Ser Gly Val Phe Ile Phe Leu Leu Ser Gly Thr Ala Gly
1               5                   10                  15

Val Leu Ser Glu Val Gln Leu His Gln Phe Gly Ala Glu Leu Val Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Asp Tyr Asn Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu
    50                  55                  60

Glu Trp Ile Gly Asp Ile Asn Pro Asn Tyr Asp Ser Thr Ser Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
                85                  90                  95

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

Tyr Tyr Cys Ala Arg Ser Arg Ser Tyr Asp Tyr Glu Gly Phe Ala Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro
    130                 135                 140

Pro Ser Val Tyr
145
```

<210> 45
<211> 132
<212> PRT
<213> Mus musculus

<400> 45

```
Ala Val Leu Arg Cys Ser Arg Gly Leu Leu Val Ile Trp Ile Ser Asp
1               5                   10                  15

Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ala Val Thr Ala Gly Glu
            20                  25                  30

Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Trp Ser Val
        35                  40                  45

Asn Gln Lys Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Gln Arg Gln Pro
    50                  55                  60

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

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Asn Val His Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln His Asn
            100                 105                 110

His Gly Ser Phe Leu Pro Ser Arg Ser Glu Gln Val Pro Ser Trp Arg
        115                 120                 125

Ser Asn Asn Arg
    130
```

<210> 46
<211> 117
<212> PRT
<213> Mus musculus

<400> 46

```
Arg Thr Thr Ser His Met Asp Ser Asp Ile Gln Leu Thr Gln Ser Pro
1               5                   10                  15

Ala Ser Leu Ser Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg
            20                  25                  30

Ala Ser Gly Asn Ile His Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Gln
        35                  40                  45

Gly Lys Ser Pro Gln Leu Leu Val Tyr Asn Ala Lys Thr Leu Ala Asp
    50                  55                  60

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser
65                  70                  75                  80

Leu Lys Ile Asn Ser Leu Gln Pro Glu Asp Phe Gly Ser Tyr Tyr Cys
                85                  90                  95

Gln His Phe Trp Ser Thr Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu
            100                 105                 110
```

```
Ile Lys Gln Ser Asp
        115
```

<210> 47
<211> 94
<212> PRT
<213> Mus musculus

<400> 47

```
Ser Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser
1               5                   10                  15

Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu
            20                  25                  30

Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe
        35                  40                  45

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val
    50                  55                  60

Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp
65                  70                  75                  80

Pro Tyr Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys Gln
                85                  90
```

<210> 48
<211> 105
<212> PRT
<213> Mus musculus

<400> 48

```
Gly Leu Phe Cys Ser Val Glu Arg Cys His Tyr Gln Leu Gln Ser Ser
1               5                   10                  15

Gln Asn Leu Leu Ser Ile Val Asn Arg Tyr His Tyr Met Ser Gly Asn
            20                  25                  30

Pro Pro Lys Leu Leu Val Tyr Pro Ala Leu Leu Ile Tyr Glu Ala Ser
        35                  40                  45

Ile Thr Lys Ser Cys Val Pro Asp Arg Phe Thr Arg Ser Gly Ser Gly
    50                  55                  60

Thr Asn Phe Thr Leu Thr Ile Asn Phe Val His Ala Asp Asp Leu Ile
65                  70                  75                  80

Phe Tyr Tyr Cys Gln His Asn Arg Gly Ser Phe Leu Pro Ser Ser Ser
                85                  90                  95

Val Gln Val Pro Arg Arg Arg Ser Asn
            100                 105
```

<210> 49

<211> 100
<212> PRT
<213> Mus musculus

<400> 49
```
Asp Ile Leu Gln Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met Asn
1               5                   10                  15

Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile Gly Leu Ile
            20                  25                  30

Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys
        35                  40                  45

Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu
    50                  55                  60

Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Trp

65                  70                  75                  80

Gly Val Trp Ser Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
                85                  90                  95

Val Ser Ser Lys
            100
```

<210> 50
<211> 90
<212> PRT
<213> Mus musculus

<400> 50
```
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Thr Ala
1               5                   10                  15

Val Ala Trp Tyr Gln Gln Lys Pro Arg Gln Ser Pro Lys Ala Leu Ile
            20                  25                  30

Tyr Leu Ala Ser Asn Arg Asp Thr Gly Leu Pro Asp Arg Phe Pro Gly
        35                  40                  45

Arg Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile Thr Asn Val Gln Ser
    50                  55                  60

Glu Asp Leu Glu Asp Tyr Phe Cys Leu Gln His Cys Asn Tyr Pro Asn
65                  70                  75                  80

Glu Phe Arg Gly Cys Thr Lys Val Pro Ile
                85                  90
```

<210> 51
<211> 116

<212> PRT
<213> Mus musculus

<400> 51

```
Leu Gln Glu Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys
1               5                   10                  15

Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Met Gln
            20                  25                  30

Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile
    35                  40                  45

Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe Lys Gly Lys
    50                  55                  60

Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu
65                  70                  75                  80

Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly
                85                  90                  95

Glu Tyr Gly Asn Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110

Val Ser Ser Asn
    115
```

<210> 52
<211> 100
<212> PRT
<213> Mus musculus

<400> 52

```
Thr Ser Asp Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala
1               5                   10                  15

Ser Gln Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly
            20                  25                  30

Lys Ser Pro Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly
    35                  40                  45

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu
    50                  55                  60

Thr Ile Ser Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys Leu
65                  70                  75                  80

Gln Tyr Asp Glu Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu
                85                  90                  95

Ile Lys Gln Lys
            100
```

<210> 53
<211> 108
<212> PRT
<213> Mus musculus

<400> 53

```
Ala Trp Leu Ser Gln Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys
1               5                   10                  15

Asp Thr Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu
            20                  25                  30

Trp Ile Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro
        35                  40                  45

Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr
    50                  55                  60

Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr
65                  70                  75                  80

Tyr Cys Ala Arg Pro Ile His Tyr Tyr Tyr Gly Ser Ser Leu Ala Tyr
                85                  90                  95

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Lys
            100                 105
```

<210> 54
<211> 104
<212> PRT
<213> Mus musculus

<400> 54

```
Glu Phe His Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg
1               5                   10                  15

Ala Ser Glu Ser Val Asp Ser Tyr Gly Asn Ser Phe Met His Trp Tyr
            20                  25                  30

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser
        35                  40                  45

Asn Leu Glu Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg
    50                  55                  60

Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala
65                  70                  75                  80

Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp Pro Gly Arg Ser Glu Val
                85                  90                  95

Val Pro Ser Trp Arg Ser Asn Lys
            100
```

<210> 55
<211> 109
<212> PRT
<213> Mus musculus

<400> 55

```
Pro Arg Ala Ser Leu Gly Val Ser Glu Thr Leu Leu Cys Thr Ser Gly
1               5                   10                  15

Phe Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly
            20                  25                  30

Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr
        35                  40                  45

Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
    50                  55                  60

Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala
65                  70                  75                  80

Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Ala Asn Trp Ala Phe Asp
                85                  90                  95

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Lys
            100                 105
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<210> 56
<211> 94
<212> PRT
<213> Mus musculus

<400> 56

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Ser Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser
1               5                   10                  15

Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu
            20                  25                  30

Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe
        35                  40                  45

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val
    50                  55                  60

Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp
65                  70                  75                  80

Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gln
                85                  90
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<210> 57
<211> 111
<212> PRT

<213> Mus musculus

<400> 57

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Pro Ala Cys Leu Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser
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Gly Phe Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro
            20                  25                  30

Gly Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Gly
        35                  40                  45

Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser
    50                  55                  60

Arg Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg
65                  70                  75                  80

Ala Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Ala Pro Leu Leu Tyr
                85                  90                  95

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
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<210> 58

<211> 102

<212> PRT

<213> Mus musculus

<400> 58

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1               5                   10                  15

Ala Ser Lys Asn Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn
            20                  25                  30

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Val Ser
        35                  40                  45

Asn Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    50                  55                  60

Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala
65                  70                  75                  80

Thr Tyr Tyr Cys Gln His Ile Arg Glu Leu Thr Arg Ser Glu Leu Val


                85                  90                  95

Pro Ser Trp Lys Ser Asn
            100
```

<210> 59

<211> 109

<212> PRT
<213> Mus musculus

<400> 59
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Pro Arg Ala Ser Leu Gly Val Ser Glu Thr Leu Leu Cys Thr Ser Gly
1               5                   10                  15

Phe Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly
            20                  25                  30

Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr
        35                  40                  45

Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
    50                  55                  60

Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala
65                  70                  75                  80

Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Ala Asn Trp Ala Phe Asp
                85                  90                  95

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Lys
            100                 105
```

<210> 60
<211> 94
<212> PRT
<213> Mus musculus

<400> 60
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Ser Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser
1               5                   10                  15

Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu
            20                  25                  30

Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe
        35                  40                  45

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val
    50                  55                  60

Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp
65                  70                  75                  80

Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gln
                85                  90
```

<210> 61
<211> 58
<212> PRT
<213> Homo sapiens

<400> 61

Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly
1 5 10 15

Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln
20 25 30

Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser
35 40 45

Glu Val Glu Ser Thr Glu Tyr Val Asn Arg
50 55

<210> 62

<211> 15

<212> PRT

<213> Homo sapiens

<400> 62

Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg
1 5 10 15

<210> 63

<211> 12

<212> PRT

<213> Homo sapiens

<400> 63

Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp
1 5 10

<210> 64

<211> 128

<212> PRT

<213> Gallus gallus

<400> 64

Ala Val Thr Leu Asp Glu Ser Gly Gly Gly Leu Gln Met Ser Arg Gly

1 5 10 15

Gly Leu Ser Leu Val Cys Lys Ala Ser Gly Phe Asp Phe Ser Ser Tyr
20 25 30

Gln Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Phe Val
35 40 45

Ala Ala Ile Asn Lys Phe Gly Asn Ser Thr Gly His Gly Ala Ala Val
50 55 60

Lys Gly Arg Val Thr Ile Ser Arg Asp Asn Gly Gln Ser Thr Val Arg
65 70 75 80

Leu Gln Leu Asn Asn Leu Arg Ala Glu Asp Thr Ala Ile Tyr Phe Cys

```
                    85                  90                  95

Thr Lys His Ala Tyr Gly Tyr Cys Gly Ser Gly Thr Trp Cys Ala Ala
                100                 105                 110

Gly Glu Ile Asp Ala Trp Gly His Gly Thr Glu Val Ile Val Ser Ser
            115                 120                 125
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<210> 65
<211> 108
<212> PRT
<213> Gallus gallus

<400> 65

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Gln Ala Ala Ser Thr Gln Pro Ser Ser Val Ser Ala Asn Pro Gly Glu
1               5                   10                  15

Thr Val Glu Ile Thr Cys Ser Gly Gly Gly Ser Tyr Ser Tyr Gly Trp
            20                  25                  30

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

Asn Asn Lys Arg Pro Ser Asp Ile Pro Ser Arg Phe Ser Gly Ser Lys
    50                  55                  60

Ser Gly Ser Thr Gly Thr Leu Thr Ile Thr Gly Val Gln Ala Asp Asp
65                  70                  75                  80

Glu Ala Val Tyr Tyr Cys Gly Ser Gly Asp Ser Thr Asp Thr Ala Val
                85                  90                  95

Phe Gly Ala Gly Thr Thr Leu Thr Val Leu Gly Gln

100                 105
```

<210> 66
<211> 12
<212> PRT
<213> Homo sapiens

<400> 66

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<210> 67
<211> 240
<212> DNA
<213> Gallus gallus

<400> 67

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gtggggctct atggggctct atggggtctc agcggggctc tgcgggctca atgggggcca     120
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cgcgaggccg tgtggcggcg gctccgtcag cgctttctgt ccttccccac agggcgcgcc 240

<210> 68
<211> 1807
<212> DNA
<213> Homo sapiens

<400> 68

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ctcgcggaca gttaagaacc caggggcctc tgcgccctgg gcccagctct gtcccacacc 180

gcggtcacat ggcaccacct ctcttgcagc ctccaccaag ggcccatcgg tcttccccct 240

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gccctccagc agcttgggca cccagaccta catctgcaac gtgaatcaca agcccagcaa 480

caccaaggtg gacaagaaag ttggtgagag gccagcacag ggagggaggg tgtctgctgg 540

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acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 1320

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<210> 69
<211> 567
<212> DNA
<213> Homo sapiens

<400> 69
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attatctggg ataagcatgc tgttttctgt ctgtccctaa catgccctgt gattatccgc 180

aaacaacaca cccaagggca gaactttgtt acttaaacac catcctgttt gcttctttcc 240

tcaggaactg tggctgcacc atctgtcttc atcttcccgc catctgatga gcagttgaaa 300

tctggaactg cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta 360

cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt cacagagcag 420

gacagcaagg acagcaccta cagcctcagc agcaccctga cgctgagcaa agcagactac 480

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aagagcttca acaggggaga gtgttag 567

<210> 70
<211> 114
<212> PRT
<213> Mus musculus

<400> 70
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1               5                   10                  15

Ala Ser Gly Phe Thr Phe Ser Asn Ser Trp Phe Asn Trp Val Arg Gln
            20                  25                  30

Ser Pro Glu Lys Gly Leu Glu Trp Val Ala Glu Ile Arg Leu Thr Ser
        35                  40                  45

Asp Asn Tyr Ala Ile Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr
    50                  55                  60

Ile Ser Arg Asp Asp Ser Lys Ser Ser Val Tyr Leu Gln Met Asn Asn
65                  70                  75                  80

Leu Arg Ala Glu Asp Thr Gly Ile Tyr Tyr Cys Thr Arg Pro Glu Thr
                85                  90                  95

Ala Arg Ala Thr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
            100                 105                 110

Ser Ser
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<210> 71
<211> 118
<212> PRT
<213> Mus musculus

<400> 71
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Pro Ala Ser Thr Ser Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu
1               5                   10                  15

Pro Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln
            20                  25                  30

Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln
        35                  40                  45

Lys Pro Gly Gln Ser Pro Lys Val Leu Ile Tyr Lys Val Phe Asn Arg
    50                  55                  60

Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
65                  70                  75                  80

Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr
                85                  90                  95

Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly Gly Thr
            100                 105                 110

Lys Leu Asn Gln Thr Gly
        115
```

# REFERENCES CITED IN THE DESCRIPTION

**Patent documents cited in the description**

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- WO2010016527A [0012]
- EP2740794A [0012]
- JP2012160763A [0126]

## Non-patent literature cited in the description

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- **ALTSCHUL et al.**Nucleic Acids Res., 1997, vol. 25, 3389-3402 [0029]
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- Molecular Cloning**SAMBROOK et al.**Current Protocols in Molecular BiologyCold Spring Harbor Laboratory Press19890000 [0031]
- A compendium of Methods from Current Protocols in Molecular Biology**AUSUBEL et al.**Short Protocols in Molecular BiologyJohn Wiley & Sons19950000 [0031]
- Antibodies: A Laboratory ManualCold Spring Harbor Laboratory19880000 [0049]
- Selected Methods in Cellular ImmunologyW.H. Freeman and Company19800000 [0049]

## Patentkrav

**1.** Fremgangsmåde til detektering af en cancer, omfattende måling af ekspressionsniveauet af CAPRIN-1 i en biologisk prøve gennem antigen-antistof-reaktion under anvendelse af et antistof, eller et antigenbindende fragment deraf, som har immunologisk reaktivitet med et polypeptid bestående af aminosyresekvensen vist i SEQ ID NO: 66.

**2.** Fremgangsmåde til detektering af en cancer ifølge krav 1, hvor det CAPRIN-1, der skal måles, er:
(a) et polypeptid med aminosyresekvensen vist i et hvilket som helst SEQ ID NO med lige nummer af SEQ ID NOs: 2 til 28 i sekvenslisten eller
(b) et polypeptid med 85 % sekvensidentitet eller højere med polypeptidet med aminosyresekvensen vist i et hvilket som helst SEQ ID NO med lige nummer af SEQ ID NOs: 2 til 28 i sekvenslisten.

**3.** Fremgangsmåde til detektering af en cancer ifølge krav 1 eller 2, hvor den biologiske prøve stammer fra et menneske, en hund eller en kat.

**4.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 3, hvor den biologiske prøve stammer fra en hund, og det CAPRIN-1, der skal måles, har aminosyresekvensen vist i SEQ ID NO: 6, 8, 10, 12 eller 14.

**5.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 3, hvor den biologiske prøve stammer fra et menneske, og det CAPRIN-1, der skal måles, har aminosyresekvensen vist i SEQ ID NO: 2 eller 4.

**6.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 5, hvor et målt CAPRIN-1-ekspressionsniveau, som er højere end niveauet hos et raskt individ, angiver tilstedeværelse af den cancer, som antistoffet er rettet mod som et terapeutisk lægemiddel mod canceren.

**7.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 6, hvor målingen af ekspressionsniveauet af CAPRIN-1 udføres under anvendelse af en immunologisk assay-fremgangsmåde.

**8.** Fremgangsmåde til detektering af en cancer ifølge krav 7, hvor den immunologiske assay-fremgangsmåde er ELISA og/eller en immunhistokemisk farvningsfremgangsmåde.

**9.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 8, hvor den biologiske prøve er en kropsvæske, et væv eller en celle.

**10.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 9, hvor canceren er mindst en cancer udvalgt fra gruppen bestående af brystcancer, hjernetumor, øsofaguscancer, mavecancer, lungecancer, levercancer, nyrecancer, cancer i skjoldbruskkirtlen, miltcancer, pancreascancer, tyktarmscancer, hudcancer, ovariecancer, livmodercancer, prostatacancer, blærecancer, testikelcancer, osteosarkom og fibrosarkom.

**11.** Fremgangsmåde til detektering af en cancer ifølge et hvilket som helst af kravene 1 til 10, hvor antistoffet eller det antigenbindende fragment deraf er et monoklonalt antistof, eller et antigenbindende fragment deraf, med en tungkæde-variabel region omfattende aminosyresekvensen vist i SEQ ID NO: 70 og en letkæde-variabel region omfattende aminosyresekvensen vist i SEQ ID NO: 71.

**12.** Anvendelse af et lægemiddel omfattende et antistof eller et antigenbindende fragment deraf, som har immunologisk reaktivitet med et polypeptid bestående af aminosyresekvensen vist i SEQ ID NO: 66 til diagnosticering af cancer, hvor anvendelsen ikke udgør en diagnosticeringsfremgangsmåde, der udføres på menneske- eller dyrekroppen.

**13.** Anvendelse af et kit omfattende et antistof eller et antigenbindende fragment deraf, som har immunologisk reaktivitet med et polypeptid bestående af aminosyresekvensen vist i SEQ ID NO: 66 til diagnosticering af cancer, hvor anvendelsen ikke udgør en diagnosticeringsfremgangsmåde, der udføres på menneske- eller dyrekroppen.

**14.** Lægemiddel omfattende et antistof, eller et antigenbindende fragment deraf, som har immunologisk reaktivitet med et polypeptid bestående af aminosyresekvensen vist i SEQ ID NO: 66, til anvendelse til diagnosticering af en cancer ved indgivelse til kroppen.

**15.** Kit omfattende et antistof, eller et antigenbindende fragment deraf, som har immunologisk reaktivitet med et polypeptid bestående af aminosyresekvensen vist i SEQ ID NO: 66, til anvendelse til diagnosticering af en cancer ved indgivelse til kroppen.

**16.** Anvendelse ifølge krav 12 eller krav 13, hvor antistoffet eller det antigenbindende fragment deraf er et monoklonalt antistof, eller et antigenbindende fragment deraf, med en tungkæde-variabel region omfattende aminosyresekvens SEQ ID NO: 70 og en letkæde-variabel region omfattende aminosyresekvensen vist i SEQ ID NO: 71.

**17.** Antistof eller antigenbindende fragment deraf til anvendelse til diagnosticering af en cancer ifølge krav 14 eller krav 15, hvor antistoffet eller det antigenbindende fragment deraf er et monoklonalt antistof, eller et antigenbindende fragment deraf, med en tungkæde-variabel region omfattende aminosyresekvensen SEQ ID NO: 70 og en letkæde-variabel region omfattende aminosyresekvensen vist i SEQ ID NO: 71.

**18.** Fremgangsmåde til udvælgelse af et individspecifikt terapeutisk lægemiddel mod en cancer, omfattende: måling af ekspressionsniveauet af CAPRIN-1 i en biologisk prøve under anvendelse af et antistof, som har immunologisk reaktivitet med et polypeptid bestående af aminosyresekvensen vist i SEQ ID NO: 66, eller et antigenbindende fragment deraf; og, hvis ekspressionsniveauet er statistisk signifikant højere end niveauet hos et raskt individ, udvælgelse af et CAPRIN-1-targeting lægemiddel som et terapeutisk lægemiddel mod en cancer, som er egnet til indgivelse til det individ, fra hvem den biologiske prøve stammer.

**19.** Fremgangsmåde til udvælgelse af et individspecifikt terapeutisk lægemiddel mod en cancer ifølge krav 18, hvor det CAPRIN-1-targeting lægemiddel er et antistof med immunologisk reaktivitet med CAPRIN-1, eller et antigenbindende fragment deraf.

# DRAWINGS

Fig. 1