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(54) **METHOD FOR DETECTING PANCREATIC CANCER**

VERFAHREN ZUR ERKENNUNG VON BAUCHSPEICHELDRÜSENKREBS

PROCÉDÉ DE DÉTECTION DU CANCER DU PANCRÉAS

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Description

Technical Field

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

Background Art

[0002] It is reported that there are over 10,000 patients with refractory pancreatic cancer in Japan, the occurrence thereof is increasing year after year, and it is assumed that the number of patients will continue to increase. Even if pancreatic cancer were surgically removed, small cancer cells have often infiltrated and metastasized to other organs. Accordingly, pancreatic cancer often relapses, and the 5-year survival rate is as low as 9%; that is, the prognosis of pancreatic cancer is very poor. For the purpose of preventing postoperative recurrence, Gemcitabine, an anticancer agent, has been employed. However, the primary purpose of Gemcitabine administration is pain relief, and tumor size reduction or survival advantage can hardly be expected. At some hospitals, another anti-cancer agent, TS-1, which is currently used for gastric cancer, is used, although it is difficult to expect any therapeutic effects.

[0003] In order to improve the prognosis for pancreatic cancer, early detection is important, as it is with other cancers; however, early detection is difficult because pancreatic cancer shows substantially no initial symptoms. To date, methods of detecting pancreatic cancer using carcinoembryonic antigen (CEA) and glycoproteins (CA19-9 and Dupan-2) in biological samples as tumor markers of pancreatic cancer have been actively employed. However, the levels of such tumor markers do not become elevated unless pancreatic cancer advances, and such markers occasionally show normal values in the progressive stage. Accordingly, such tumor markers are not considered to be sufficient for accurate detection of pancreatic cancer. In addition, most tumor markers that are currently known are present in very small amounts in the body fluids (at the pg/ml level). In order to detect such small amounts of markers, accordingly, detection techniques with high sensitivity or special techniques are necessary. Under such circumstances, a novel technique for detecting pancreatic cancer in a simple manner with high sensitivity is expected to be applicable to diagnosis of pancreatic cancer. It is necessary to undergo periodic thorough examinations in order to detect early-stage pancreatic cancer. Accordingly, a method of detecting cancer that can be carried out in a simple manner with the use of blood serum or urine samples without the imposition of physical or financial burdens on either healthy individuals without pancreatic cancer or patients with cancer has been awaited.

[0004] Also, pancreatic cancer is refractory in dogs. Although a lump can be observed in the abdominal region of a dog afflicted with pancreatic cancer, the major symptoms are rapid energy loss, unsteady gait, and gait abnormalities resulting from hypoglycemia. In most cases, the development of cancer would not be detected until such symptoms are observed. In addition, pancreatic cancer is often likely already to be in the advanced stage when such symptoms are observed. In addition to surgical removal of pancreatic cancer, accordingly, therapeutic techniques are limited to supportive therapy and administration of anticancer agents. As with the case of human patients, early detection is important for dogs afflicted with pancreatic cancer in order to effectively treat such pancreatic cancer. As with the case for humans, there were no diagnostic agents for dogs in the past that allowed detection of pancreatic cancer at the early stage in a simple manner. In the field of veterinary medicine, detection techniques such as radiographic techniques by means of X-rays, CT, or MRI have not yet become common. At present, detection is carried out by palpation, simple blood testing, and X-ray photography, and diagnosis is heavily dependent on the experience of veterinary doctors. If a simple means for cancer detection with high sensitivity that can be applied to diagnosis of pancreatic cancer in dogs is provided, adequate treatment can be performed, which has great advantages for dog owners and veterinary doctors.

[0005] Cytoplasmic- and proliferation-associated protein 1 (CAPRIN-1) is an intracellular protein that is expressed when normal cells in the resting phase are activated or undergo cell division. CAPRIN-1 is also known to be involved in the control of the transport and translation of mRNAs through formation of cytoplasmic stress granules and RNA in a cell. Also, genes encoding CAPRIN-1 proteins are demonstrated to be expressed specifically in canine and human testis and malignant tumor cells, FCM analysis of breast cancer cells with the use of antibodies against CAPRIN-1 demonstrates CAPRIN-1 expression on the surfaces of breast cancer cells, and immunohistochemical staining using breast cancer tissues demonstrates CAPRIN-1 expression at high level in breast cancer cells. In addition, it has been reported that the antibodies mentioned above would damage breast cancer cells through the functions of lymphocytes, and that antibodies against CAPRIN-1 exert potent antitumor effects in cancer-carrying mouse models into which breast cancer cells had been transplanted (Patent Literature 1). Also, it has been reported that cancers such as breast cancer could be diagnosed by measuring either antibodies induced in the body of a subject against CAPRIN-1 present in the blood serum or polypeptides that undergo antigen-antibody reactions with CAPRIN-1 (Patent Literature 2). Up to the present, however, there have been no reports of the fact that pancreatic cancer can be diagnosed by measuring either antibodies against CAPRIN-1 induced in the blood serum of a patient with pancreatic cancer or polypeptides that undergo antigen-antibody reactions with the CAPRIN-1.

Prior Art Literatures

Patent Literature

[0006]

Patent Literature 1: International Publication No. WO 2010/016526
Patent Literature 2: International Publication No. WO 2010/016527

Summary of the Invention

Problem to Be Attained by the Invention

[0007] It is an object of the present invention to provide a means for detecting pancreatic cancer that is useful for diagnosis of pancreatic cancer.

Means for Solving the Problem

[0008] The present inventors have conducted concentrated studies. As a result, the present inventors have now found that pancreatic cancer can be diagnosed, examined, or detected on the basis of CAPRIN-1 expression in pancreatic cancer, measurement (or assay) of antibodies against CAPRIN-1 induced in the blood serum of a patient with pancreatic cancer with the use of a CAPRIN-1 protein, and binding of the antibodies produced with the use of such proteins to CAPRIN-1 in the pancreatic cancer tissue. This has led to the completion of the present invention.

[0009] Specifically, the present invention provides a method as defined in the claims for detecting pancreatic cancer comprising measuring a CAPRIN-1 expression in a sample separated from a subject. The term "detecting" as used herein can be used interchangeably with the term "examining" or "evaluating." Also, the present disclosure provides a reagent or kit for detecting pancreatic cancer comprising a polypeptide that undergoes an antigen-antibody reaction with an antibody against CAPRIN-1 induced or elicited in the body of a subject. Further, the present disclosure provides a reagent or kit for detecting pancreatic cancer comprising an antibody that undergoes an antigen-antibody reaction with CAPRIN-1 or an antigen-binding fragment of the antibody. Furthermore, the present disclosure provides a reagent or kit for detecting pancreatic cancer comprising a polynucleotide hybridizing specifically to a partial sequence comprising at least 15 to 19 nucleotides or at least 20 to 30 nucleotides of the nucleotide sequence represented by any of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, ...,29. The "reagent or kit for detecting pancreatic cancer" used herein can also be referred to as a "reagent or kit for pancreatic cancer detection."

[0010] Specifically, the present invention provides methods, as defined in the claims, for detecting pancreatic cancer.

[0011] According to the present invention, a novel method for detecting pancreatic cancer is provided. As specifically described in the examples below, a recombinant polypeptide prepared based on the amino acid sequence of CAPRIN-1 (or Caprin-1) is capable of specifically reacting with an antibody that exists in the serum of a patient with pancreatic cancer. As such, the pancreatic cancer existing in a subject can be detected by measuring the antibody in a sample by the method of the present invention. Also, pancreatic cancer existing in a subject can be detected by measuring (or assaying) CAPRIN-1 itself. As described in the examples below, in addition, high levels of CAPRIN-1 gene expression are observed specifically in testis and pancreatic cancer cells of subjects (hereinafter, such expression product is occasionally referred to as a "nucleic acid encoding a CAPRIN-1 (protein)"). Therefore, pancreatic cancer can also be detected by measuring a nucleic acid. Further, the presence or amount of CAPRIN-1 (expression) in the pancreatic cancer tissue can be measured with the use of an antibody against CAPRIN-1. Patients with pancreatic cancer may be subjected to such measurement in advance, so that the patients to whom a CAPRIN-1-targeted therapeutic agent (e.g., antibody medicine) is applicable can be selected.

Embodiments for Carrying out the Invention

[0012] According to the method of the present invention, the presence or an amount of CAPRIN-1 (expression) is measured using a sample separated from a subject. Examples of methods for measuring the presence or an amount of CAPRIN-1 (expression) include: a method for immunologically measuring an antibody against CAPRIN-1 contained in a sample (the first method); a method for immunologically measuring CAPRIN-1 itself contained in a sample (the second method); and a method for measuring a nucleic acid encoding CAPRIN-1 contained in a sample, such as mRNA or cDNA synthesized from mRNA (the third method). In the present invention, the presence or an amount of CAPRIN-1 (expression) may be measured by any of the above methods. In the present invention, the term "measuring" is intended to include any of the following meaning: detecting, qualitatively measuring, quantitatively measuring, and semi-quanti-

tatively measuring.

[0013] The amino acid sequence represented by SEQ ID NOs: 6, 8, 10, 12, or 14 is an amino acid sequence of canine CAPRIN-1. Canine CAPRIN-1 having such an amino acid sequence has been identified as a polypeptide binding to an antibody specifically existing in the serum derived from a cancer-bearing dog (see Example 1). An antibody against CAPRIN-1 having the amino acid sequence represented by SEQ ID NO: 6, 8, 10, 12, or 14 is specifically induced or elicited in the body of a cancer-bearing dog. Specifically, canine pancreatic cancer can be detected by measuring the above antibody against CAPRIN-1 having the amino acid sequence represented by SEQ ID NO: 6, 8, 10, 12, or 14 by the first method. Also, canine pancreatic cancer can be detected by measuring CAPRIN-1 itself as an antigen having the amino acid sequence represented by SEQ ID NO: 6, 8, 10, 12, or 14 by the second method. Since the CAPRIN-1 gene is expressed at significantly high levels in pancreatic cancer cells, canine pancreatic cancer can be detected by measuring the nucleic acid in accordance with the third method.

[0014] The term "having an amino acid sequence" used herein refers to amino acid residues aligned in a given order. Therefore, for example, the expression "polypeptide having the amino acid sequence represented by SEQ ID NO: 2" refers to a polypeptide having 709 amino acid residues, which consists of the amino acid sequence of Met Pro Ser Ala ... (partially omitted) ... Gln Gln Val Asn represented by SEQ ID NO: 2. Also, the expression "polypeptide having the amino acid sequence represented by SEQ ID NO: 2" may also be abbreviated as "the polypeptide of SEQ ID NO: 2," for example. The same applies to the expression "having a/ nucleotide sequence." In this case, the term "having" may be substituted with the expression "comprising" or "consisting of."

[0015] Also, the term "polypeptide" used herein refers to a molecule that is formed via a peptide bond of a plurality of amino acids. Examples of such molecule include not only polypeptide molecules with large numbers of constituent amino acids, but also low-molecular-weight molecules (oligopeptides) with small numbers of amino acids and full-length proteins. The present invention further encompasses full-length CAPRIN-1 proteins each having an amino acid sequence represented by any of the even-numbered SEQ ID NOs: 2 to 30 (i.e., SEQ ID NOs: 2, 4, 6,...26, 28, and 30).

[0016] The term "subject" used herein refers to vertebrates, including mammals and birds, preferably mammals, and more preferably humans, dogs, cows, and horses.

[0017] The term "sample" used herein refers to a biological sample subjected to examination aimed at detection of pancreatic cancer. Examples of the sample include body fluids, tissues, and cells separated from a subject. Examples of body fluids include, but are not limited to, blood, serum, blood plasma, ascites fluid, and pleural effusion. Tissues or cells of the pancreas that is suspected of being afflicted with cancer are within the scope of the "sample."

[0018] In the method of the present invention, the targets to be measured are to not only canine CAPRIN-1 of SEQ ID NO: 6, 8, 10, 12, or 14, but also CAPRIN-1 of other mammals (hereinafter, which may also be referred to as a "homolog" (or "ortholog") for canine CAPRIN-1). When it is simply referred to as "CAPRIN-1," CAPRIN-1 from another mammal, including a human, is also a target to be measured, in addition to CAPRIN-1 from a dog. As specifically described in the examples below, the human CAPRIN-1 gene expression level is significantly high in human pancreatic cancer cells, whereas no antibody against human CAPRIN-1 gene is detected in a healthy human body. As such, pancreatic cancer of a mammal other than a dog can be detected by measuring CAPRIN-1 expression in the mammal. An example of CAPRIN-1 of a mammal other than a dog to be measured by the method of the present invention is, but is not limited to, human CAPRIN-1. Nucleotide sequences encoding human CAPRIN-1 and amino acid sequences therefor are represented by SEQ ID NOs: 1 and 3 and SEQ ID NOs: 2 and 4 in the Sequence Listing. Sequence identity between human CAPRIN-1 and canine CAPRIN-1 is 94% for nucleotide sequence and is 98% for amino acid sequence. The sequence identity of the amino acid sequences of CAPRIN-1 is as high as 98% between genetically distant mammals, such as a dog and a human. Therefore, it is considered that the sequence identity is about 85% or higher between a dog and a mammal other than a human; that is, canine CAPRIN-1 and its homolog. CAPRIN-1, the expression of which is to be measured by the method of the present invention, preferably has 85% or higher, more preferably 90% or higher, and further preferably 95% or higher sequence identity with the amino acid sequence of canine CAPRIN-1 represented by SEQ ID NO: 6, 8, 10, 12, or 14, although the sequence identities are not limited thereto.

[0019] In the first method, the antibody that can be present in a sample can be easily measured by immunoassay using an antigenic substance that undergoes an antigen-antibody reaction with the antibody. Immunoassay itself is a well-known conventional method as specifically described below. As an antigenic substance for immunoassay, for example, the canine CAPRIN-1 protein of SEQ ID NO: 6, 8, 10, 12, or 14 that induces the antibody within the body of a cancer-bearing dog or a fragment containing an epitope of such protein can be used. Further, the antibody has a cross-reactivity. A molecule other than an antigenic substance that actually serves as an immunogen can also bind, via an antigen-antibody reaction, to an antibody induced against an immunogen, as long as the molecule has a structure analogous to an epitope of the immunogen. Between a protein from a certain type of mammal and a homolog thereof from another mammal, in particular, the identity of their amino acid sequences is high, and epitope structures are often analogous to each other. As specifically described in the examples below, the canine CAPRIN-1 of SEQ ID NO: 6, 8, 10, 12, or 14 undergoes an antigen-antibody reaction with an antibody induced against the canine CAPRIN-1 within the body of a cancer-bearing dog. Also, human CAPRIN-1 undergoes an antigen-antibody reaction with the antibody induced

within the body of a cancer-bearing dog. Accordingly, CAPRIN-1 from any mammal can be used as an antigen for immunoassay in accordance with the first method of the present invention.

[0020] When an antigenic substance is a protein or the like having a complicated structure and a high molecular weight, in general, a plurality of sites having different structures are present on the molecule. Therefore, a plurality of types of antibodies capable of recognizing and binding to different sites of such antigenic substances are produced in the body of a subject. Specifically, an antibody that is produced in the subject against an antigenic substance such as a protein is a polyclonal antibody that is a mixture of a plurality of types of antibodies. An antibody now found by the present inventors is also a polyclonal antibody that is specifically present in the serum obtained from a cancer-bearing subject and specifically binds, via an antigen-antibody reaction, to a recombinant CAPRIN-1 protein. The term "polyclonal antibody" used in the present invention refers to an antibody that exists in the serum obtained from a subject containing an antigenic substance and is induced against such antigenic substance.

[0021] In the examples below, polypeptides of SEQ ID NO: 6 and SEQ ID NO: 8 (both, canine CAPRIN-1) and the polypeptide of SEQ ID NO: 2 (human CAPRIN-1) were prepared as antigens for immunoassay of specific antibodies in cancer-bearing living animals. The reactivity between these polypeptides and the antibodies in the serum obtained from a cancer-bearing subject was then confirmed. However, the antibodies mentioned above iare polyclonal antibodies, and they naturally bind to polypeptides consisting of homologs of SEQ ID NO: 6, 8, and 2. Even in the case of a fragment of such a polypeptide, it can bind to an antibody contained in the serum obtained from a cancer-bearing subject since some polyclonal antibodies are capable of recognizing the structure of the fragment. That is, both the polypeptide (that is, the full-length CAPRIN-1 protein) of the homolog of SEQ ID NO: 6, 8, or 2 and a fragment thereof can be similarly used for assay of a polyclonal antibody contained specifically in the serum of a cancer-bearing subject, and they are useful for cancer detection. Accordingly, a polypeptide to be used as an antigen for immunoassay in the first method of the present invention is not limited to a polypeptide alone consisting of the full-length region of a CAPRIN-1 protein (e.g., SEQ ID NO: 6, 8, or 2). It can be a polypeptide fragment consisting of at least 7 to 12, and preferably at least 8, 9, or 10 continuous amino acids of the amino acid sequence of a CAPRIN-1 protein that undergoes an antigen-antibody reaction with a polyclonal antibody against the CAPRIN-1 protein (hereinafter, it may be referred to as a "specifically reactive partial polypeptide" for convenience). It is known in the art that a polypeptide comprising about 7 to 12 or more amino acid residues can exert antigenicity. If the number of amino acid residues is too low, however, such polypeptide is highly likely to cross-react with an antibody against a protein other than the CAPRIN-1 protein that exists in the sample. In view of enhancing the accuracy of immunoassay, accordingly, the number of amino acid residues of a polypeptide fragment is preferably 20 or more, 30 or more, and 50 or more, more preferably 100 or more or 150 or more, further preferably 300 or more, and even further preferably 600 or more. The number of amino acid residues may be 1,000 or more, or 1,500 or more.

[0022] Preferable examples of the polypeptides to be used as antigens include the polypeptides of the even-numbered SEQ ID NOs: 2 to 30 or fragments thereof comprising epitopes (e.g., a polypeptide fragment comprising about 7 to 12 or more amino acid residues).

[0023] Nucleotide sequences of polynucleotides encoding proteins consisting of the amino acid sequences of the even-numbered SEQ ID NOs: 2 to 30 (i.e., SEQ ID NOs: 2, 4, 6...28, and 30) are represented by the odd-numbered SEQ ID NOs: 1 to 29 (i.e., SEQ ID NOs: 1, 3, 5...27, and 29).

[0024] In general, it is well known in the art that protein antigens retain antigenicity almost equivalent to that of the original protein even if a small number of amino acid residues have been substituted, deleted, added, or inserted in the amino acid sequence of the protein. Therefore, a polypeptide having a sequence derived from the amino acid sequence of a CAPRIN-1 protein by substitution, deletion, and/or insertion of a small number of (preferably one or several) amino acid residues, having 80% or higher, 85-90% or higher, preferably 90% or higher, more preferably 95% or higher, further preferably 98% or higher, and still further preferably 99% or higher sequence identity with the original sequence, and specifically binding via an antigen-antibody reaction to an antibody against CAPRIN-1 (hereinafter, the same may be referred to as a "specifically reactive modified polypeptide" for convenience) can be used for cancer detection in a manner similar to the case of the polypeptides described above. Preferably, a specifically reactive modified polypeptide has an amino acid sequence derived from the amino acid sequence of a CAPRIN-1 protein by substitution, deletion, and/or insertion of one 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, and further preferably an integer of 2 to 4.

[0025] The term "sequence identity" used herein with reference to amino acid sequences is determined by aligning two amino acid sequences to be compared, so that as many amino acid residues match as possible, dividing the number of amino acid residues that match by the total number of amino acid residues, and then expressing the results in percentage terms (%). Upon the above alignment, gaps are inserted as appropriate into one or both of the sequences to be compared, according to need. Such sequence alignment can be performed using a well-known program or algorism, such as BLAST, FASTA, or CLUSTAL W (Karlin and Altschul, Proc. Natl. Acad. Sci. U.S.A., 87: 2264-2268, 1993; Altschul et al., Nucleic Acids Res., 25: 3389-3402, 1997).

[0026] Twenty types of amino acids constituting naturally occurring proteins can be divided into groups of amino acids

having properties analogous to each other: neutral amino acids having side chains with low polarity (Gly, Ile, Val, Leu, Ala, Met, and Pro); neutral amino acids having hydrophilic side chains (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 among these amino acids (that is, conservative substitution) rarely alters the properties of the resulting polypeptide. When amino acid residues of CAPRIN-1 are to be substituted, accordingly, substitution is performed between members of the same group, so that the possibility of maintaining binding with the corresponding antibody becomes higher. In the present invention, however, the above variant may involve non-conservative substitution, as long as immunity-inducing activity equivalent to or almost equivalent to that of an unmodified polypeptide is imparted.

[0027] A polypeptide (hereinafter, which may be referred to as a "specifically reactive addition polypeptide" for convenience) that contains, as a partial sequence, the above polypeptide to be used in the present invention (e.g., prepared by addition of another (poly)peptide to one end or both ends of a polypeptide to be used in the present invention) and specifically binds via an antigen-antibody reaction to an antibody against CAPRIN-1 can also be used for detection of pancreatic cancer in a manner similar to the cases of the above polypeptides.

[0028] The polypeptides used in the present invention can be synthesized in accordance with a chemical synthesis method such as the Fmoc method (the fluorenylmethyloxycarbonyl method) or the tBoc method (the t-butyloxy-carbonyl method) (the Japanese Biochemical Society (ed.), Seikagaku Jikken Koza (Biochemical Experimental Lecture Series) 1, Tanpakushitsu no Kagaku (Protein Chemistry) IV, Kagaku Shushoku to Peptide Gousei (Chemical Modification and Peptide Synthesis), TOKYO KAGAKU DOZIN CO., LTD, Japan, 1981). Also, the polypeptides can be synthesized by a conventional method using various commercially available peptide synthesizers. Alternatively, the polypeptides can be easily prepared by known genetic engineering techniques (e.g., Sambrook et al., Molecular Cloning, 2nd Edition, Current Protocols in Molecular Biology, 1989, Cold Spring Harbor Laboratory Press; Ausubel et al., Short Protocols in Molecular Biology, 3rd Edition, A Compendium of Methods from Current Protocols in Molecular Biology, 1995, John Wiley & Sons). From RNA extracted from a tissue expressing a gene encoding the human CAPRIN-1 of SEQ ID NO: 2 or a homolog thereof, for example, cDNA of the gene is prepared via RT-PCR, the full-length sequence or a desired partial sequence of the cDNA is incorporated into an expression vector, and the vector is then introduced into a host cell. Thus, a polypeptide of interest can be obtained. The nucleotide sequences of cDNAs encoding canine CAPRIN-1 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 human homologs thereof; that is, the cDNAs encoding human CAPRIN-1 of SEQ ID NOs: 2 and 4, are shown in SEQ ID NOs: 1 and 3, respectively. Accordingly, primers used for RT-PCR can be easily designed with reference to these nucleotide sequences. As described below, also, a gene encoding CAPRIN-1 of a non-human mammal can be amplified using primers designed with reference to the nucleotide sequences of the odd-numbered SEQ ID NOs: 1 to 29. Accordingly, cDNA encoding, for example, feline CAPRIN-1 can be easily prepared by techniques similar to the above techniques. RNA extraction, RT-PCR, incorporation of cDNA into a vector, and introduction of a vector into a host cell can be performed by, for example, well-known methods as described below. Also, vectors and host cells used herein are well known, and various vectors and host cells are commercially available.

[0029] The above host cells may be any cells, as long as they can express the above polypeptides. Examples of prokaryotic host cells include Escherichia coli. Examples of eukaryotic host cells include cultured mammalian cells, such as monkey kidney cells (COS1), Chinese hamster ovary cells (CHO), the human embryonic kidney cell line (HEK293), and the mouse embryonic skin cell line (NIH3T3), budding yeast, fission yeast, silkworm cells, and Xenopusoocytes.

[0030] When prokaryotic cells are used as host cells, an expression vector having a replication origin in prokaryotic cells, a promoter, a ribosome-binding site, a multi-cloning site, a terminator, a drug-resistance gene, an auxotrophic complementary gene, and the like is used. Examples of expression vectors for Escherichia coli include pUC vectors, pBluescriptII, pET expression systems, and pGEX expression systems. DNA encoding the above polypeptide is incorporated into such an expression vector, prokaryotic host cells are transformed with the vector, and the thus obtained transformant is cultured. Thus, the polypeptide encoded by the DNA can be expressed in the prokaryotic host cells. At this time, the polypeptide can also be expressed as a fusion protein with another protein. DNA encoding the above polypeptide can be obtained by preparing cDNA by, for example, RT-PCR, as described above. Alternatively, such DNA can be synthesized by a conventional technique using a commercially available nucleic acid synthesizer, as described below. The nucleotide sequences of cDNAs of the genes encoding CAPRIN-1 of SEQ ID NOs: 2 and 4 are shown in SEQ ID NOs: 1 and 3 in the Sequence Listing, respectively.

[0031] When eukaryotic cells are used as host cells, an expression vector for eukaryotic cells having a promoter, a splicing region, a poly(A) additional site, and the like is used. Examples of such an expression vector include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, an EBV vector, pRS, pcDNA3, and pYES2. As described above, DNA encoding a polypeptide used in the present invention is incorporated into such an expression vector, eukaryotic host cells are transformed with the vector, and the thus obtained transformant is cultured. Thus, the polypeptide encoded by the above DNA can be expressed in eukaryotic host cells. When pIND/V5-His, pFLAG-CMV-2, pEGFP-N1, pEGFP-C1, or the like is used as an expression vector, the above polypeptide can be expressed as a fusion protein with various tags, such as His tags (e.g., $(His)_6$ to $(His)_{10}$), a FLAG tag, a myc tag, an HA tag, or GFP.

[0032] An expression vector can be introduced into a host cell in accordance with a well-known technique, such as electroporation, a calcium phosphate method, a liposome method, a DEAE dextran method, microinjection, viral infection, lipofection, or binding with a cell-membrane-permeable peptide.

[0033] A polypeptide of interest can be isolated and purified from host cells using known isolation techniques in combination. Examples of such techniques include treatment using a denaturing agent such as urea or a surfactant, ultrasonication, enzymatic digestion, salting-out, solvent fractionation and precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion exchange chromatography, hydrophobic chromatography, affinity chromatography, and reverse phase chromatography.

[0034] Polypeptides obtained by the above methods include polypeptides in the form of fusion proteins with any other proteins. Examples of such fusion proteins include a fusion protein with glutathione-S-transferase (GST) and a fusion protein with a His tag. Polypeptides in the form of such fusion proteins are also within the scope of the above described specifically reactive addition polypeptides, and such polypeptides can be used for the first detection method of the present invention. Further, polypeptides expressed in transformed cells may occasionally be subjected to various types of modification within cells after translation. Such a post-translationally modified polypeptide can be used in the first detection method of the present invention, as long as it is capable of specifically binding, via an antigen-antibody reaction, to an antibody against a CAPRIN-1 protein. Examples of such post-translational modification include the removal of N-terminal methionine, N-terminal acetylation, glycosylation, limited proteolysis by intracellular protease, myristoylation, isoprenylation, and phosphorylation.

[0035] An antibody in a sample can be easily measured by immunoassay using the above polypeptide as an antigen. Immunoassay itself is well known in the art. Immunoassay is classified into the sandwich method, the competition method, the agglutination method, the Western blot method, and the like based on types of reactions. Also, immunoassay is classified based on labels into radioimmunoassay, fluorescence immunoassay, enzyme immunoassay, and biotin immunoassay, for example. Immunoassay of the above antibody can be performed using any of these methods. Sandwich ELISA or the agglutination method are preferably employed as an immunoassay technique for the above antibody in the method of the present invention, since the procedures of these methods are convenient and require no extensive apparatus and the like, although techniques are not limited thereto. When an enzyme is used as a label for an antibody, such enzyme is not particularly limited, as long as it satisfies conditions such that: the turnover number is high; it remains stable even if it is bound to an antibody; and it specifically causes the color development of the substrate. Enzymes that can be used for general enzyme immunoassay, such as peroxidase, β-galactosidase, alkaline phosphatase, glucose oxidase, acetylcholine esterase, glucose-6-phosphorylation dehydrogenase, and malic acid dehydrogenase, can be used. In addition, enzyme-inhibiting substances, coenzymes, and the like can be used. Binding of these enzymes with antibodies can be performed by known methods involving the use of a cross-linking agent, such as a maleimide compound, the biotin-(strept)avidin system, or the like. As a substrate, a known substance can be used depending on the type of an enzyme to be used. When peroxidase is used as an enzyme, for example, 3,3',5,5'-tetramethylbenzidine can be used. When alkaline phosphatase is used, for example, para-nitrophenol can be used. A radioisotope that is generally used for radioimmunoassay, such as ^{125}I or ^{3}H, can be used. A fluorescent dye that is used for general fluorescent antibody techniques, such as fluorescence isothiocyanate (FITC), tetramethylrhodamine isothiocyanate (TRITC), or a cyanine fluorescence dye (e.g., Cy3 or Cy5), can be used.

[0036] There is no need to explain the above immunoassay techniques herein since these techniques are well known; however, briefly, for example, the sandwich method comprises immobilizing the above polypeptide used as an antigen on a solid phase, allowing the polypeptide to react with a sample such as serum, washing, allowing an appropriate secondary antibody to react with an antibody from the sample, again washing, and then measuring the secondary antibody bound to the solid phase. By immobilizing an antigenic polypeptide on a solid phase, an unbound secondary antibody can be easily removed. Accordingly, it is preferable as an embodiment of the method for detecting cancer of the present invention. As a secondary antibody, an anti-canine IgG antibody, for example, can be used if a sample is from a dog. A secondary antibody is labeled in advance with a labeling substance exemplified above, so that the secondary antibody bound to a solid phase can be measured. The amount of the secondary antibody thus measured corresponds to the amount of the above antibody in the serum sample. When an enzyme is used as a labeling substance, the amount of the antibody can be measured by adding a substrate that is degraded in order to develop color by enzymatic action and then optically measuring the amount of the substrate degraded. When a radioisotope is used as a labeling substance, the amount of radiation from the radioisotope can be measured using a scintillation counter or the like.

[0037] In the second method of the present invention, CAPRIN-1 that can be contained in a sample obtained from a subject is measured. As described above, the amount of an antibody that undergoes an antigen-antibody reaction with CAPRIN-1 of a dog, a human, or the like is significantly higher in subjects with pancreatic cancer, compared with healthy subjects. This indicates that the amount of CAPRIN-1 accumulated as an antigen is significantly high in pancreatic cancer cells. In the case of healthy subjects, the CAPRIN-1 expression level is below the detection limit, or CAPRIN-1 expression in tissue is weak and it might occur merely within cells. Pancreatic cancer can also be detected by directly measuring CAPRIN-1, as specifically described in the examples below. Therefore, pancreatic cancer can be detected

in a subject by measuring CAPRIN-1 itself, as in the case of the first method.

[0038] A polypeptide in a sample can be easily measured by well-known immunoassay techniques. Specifically, an antibody that undergoes an antigen-antibody reaction with CAPRIN-1 or an antigen-binding fragment thereof is prepared, and immunoassay is carried out using the same. Thus, the presence of CAPRIN-1 in the sample can be measured. As described above, an antibody has cross-reactivity. With the use of an antibody that undergoes an antigen-antibody reaction with canine CAPRIN-1 of SEQ ID NO: 6 or an antigen-binding fragment thereof, accordingly, not only the canine CAPRIN-1 of SEQ ID NO: 6, but also its homologs in other mammals (e.g., the human CAPRIN-1 of SEQ ID NO: 2 or 4) can be measured. The immunoassay technique itself is a well-known conventional technique, as described above.

[0039] This study reveals that CAPRIN-1 is a cell membrane protein that is expressed on the surface of pancreatic cancer cells. A subject with cancer contains many proteases in cancer tissues. Accordingly, the portion of the CAPRIN-1 sequence expressed outside the cancer cells is degraded and separated from the cancer cells, and such portion is larger in amount than the portion of the CAPRIN-1 sequence expressed in the cancer cells. If an antibody capable of binding to the surfaces of pancreatic cancer cells is used as an antibody against CAPRIN-1 in the measurement, or if an antigen-binding fragment thereof is used, accordingly, a larger amount of CAPRIN-1 can be detected, and pancreatic cancer can be diagnosed with higher sensitivity.

[0040] In the present invention, accordingly, use of an antibody that binds to a portion expressed on the surface of a pancreatic cancer cell of a CAPRIN-1 protein molecule is preferable. An example of a partial peptide of a CAPRIN-1 protein expressed on the surface of a pancreatic cancer cell is a polypeptide consisting of an amino acid sequence of 7 to 12 or more continuous amino acid residues within the region of amino acid residues (aa) 50 to 98 or amino acid residues (aa) 233 to 305 in any of the amino acid sequences represented by even-numbered SEQ ID NOs: 2 to 30 in the Sequence Listing, excluding SEQ ID NO: 6 and SEQ ID NO: 18. A specific example thereof is, but is not limited to, the amino acid sequence represented by SEQ ID NO: 43 or SEQ ID NO: 61 (in the amino acid sequence represented by SEQ ID NO: 61, a region of the amino acid sequence represented by SEQ ID NO: 62 or SEQ ID NO: 63 is preferable) or an amino acid sequence having 80% or higher, preferably 85% or higher, more preferably 90% or higher, and further preferably 95% or higher sequence identity with the relevant amino acid sequence. In addition, all antibodies binding to these polypeptides fall within the scope of the antibodies used in the present invention. Specific examples include an antibody binding to a polypeptide comprising the amino acid sequence represented by SEQ ID NO: 43 or antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 44 and 45 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 44 and 46 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 44 and 47 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 44 and 48 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 49 and 50 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 51 and 52 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 53 and 54 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 55 and 56 or an antigen-binding fragment thereof, a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 57 and 58 or an antigen-binding fragment thereof, and a monoclonal antibody having the amino acid sequences represented by SEQ ID NOs: 59 and 60 or an antigen-binding fragment thereof.

[0041] The term "antigen-binding fragment" used herein refers to an antibody fragment capable of binding to an antigen, such as an Fab fragment, an $F(ab')_2$ fragment, or an Fv fragment, contained in an antibody molecule. An antibody may be a polyclonal antibody or a monoclonal antibody. For immunoassay, a monoclonal antibody with high reproducibility is preferable. Methods for preparing a polyclonal antibody and a monoclonal antibody using a polypeptide as an immunogen are well known and can be easily performed in a conventional manner. For example, an animal is immunized with CAPRIN-1 or a fragment thereof alone or CAPRIN-1 or a fragment thereof bound to a carrier protein, such as keyhole limpet hemocyanin (KLH), casein, or serum albumin, as an immunogen, together with an adjuvant, and an antibody against CAPRIN-1 can then be induced. Antibody-producing cells, such as splenocytes or lymphocytes, collected from the immunized animal are fused to myeloma cells to prepare hybridomas, and hybridomas producing an antibody that binds to CAPRIN-1 are selected and then grown. Thus, a monoclonal antibody whose corresponding antigen is CAPRIN-1 can be obtained from the culture supernatant. The method described above is a well-known conventional method.

[0042] In the third method of the present invention, a nucleic acid encoding CAPRIN-1 (e.g., mRNA or cDNA synthesized from mRNA) that can be contained in a sample obtained from a living organism is measured. As specifically described in the examples below, a nucleic acid encoding the canine CAPRIN-1 of SEQ ID NO: 6, 8, 10, 12, or 14 or human CAPRIN-1 of SEQ ID NO: 2 or 4 is expressed at a significantly high level in pancreatic cancer cells. Therefore, a cancer existing in the living body can be detected by measuring such nucleic acid in a sample.

[0043] mRNA in a sample can be quantitatively measured by, for example, a conventional method, such as real-time detection RT-PCR using the mRNA as a template. Such mRNA can generally be quantitatively measured based on

staining intensity or the like in the conventional Northern blot method. The cDNA sequences encoding CAPRIN-1 of the even-numbered SEQ ID NOs: 2 to 30 are represented by the odd-numbered SEQ ID NOs: 1 to 29, respectively. Accordingly, a polynucleotide specifically hybridizing to a partial region in the nucleotide sequence represented by any of the odd-numbered SEQ ID NOs: 1 to 29 (hereinafter, referred to as a "polynucleotide for cancer detection") is prepared based on these sequences, and such polynucleotide is used as a probe or a primer for nucleic acid amplification to determine the amount of the mRNA in a sample. If a polynucleotide is capable of specifically hybridizing to a partial region in the nucleotide sequence represented by any of the odd-numbered SEQ ID NOs: 1 to 29, mRNA encoding CAPRIN-1 in mammals other than dogs and humans can also be measured, as described later. In the present invention, a polynucleotide may be RNA or DNA.

[0044] The term "specifically hybridizing to" used herein refers to a situation in which said polynucleotide hybridizes only to a target partial region and does not substantially hybridize to any other regions under stringent hybridization conditions.

[0045] The term "under stringent hybridization conditions" used herein refers to conditions employed for annealing in general PCR or detection using a probe. In the case of PCR using Taq polymerase, for example, a reaction is performed at an appropriate annealing temperature ranging from about 54°C to 60°C using a general buffer, such as a buffer containing 50 mM KCl, 10 mM Tris-HCl (pH 8.3 to 9.0), and 1.5 mM $MgCl_2$. In the case of Northern hybridization, for example, a reaction is performed using a general hybridization solution such as 5x SSPE, 50% formamide, 5x Denhardt's solution, and 0.1-0.5% SDS, or 0.1-5x SSC and 0.1-0.5% SDS at an appropriate hybridization temperature ranging from about 42-65°C. After hybridization, washing is performed with, for example, 0.1-0.2x SSC and 0.1% SDS. Appropriate annealing temperatures or hybridization temperatures are not limited to the above examples, and such temperatures are determined based on the Tm value for a polynucleotide for cancer detection that is used as a primer or a probe and the empirical rules of experimenters. A person skilled in the art can easily determine such temperature range.

[0046] The expression "does not substantially hybridize to" used herein refers to a situation in which said polynucleotide does not hybridize to a target partial region at all or a extremely low amount of the polynucleotide hybridizes to a target partial region, that is, in a relatively negligible amount, even when it hybridizes to a target partial region. An example of the polynucleotide specifically hybridizing under such conditions is a polynucleotide having a certain level or higher of a sequence identity with the nucleotide sequence of a target partial region. For example, such polynucleotide has 70% or higher, preferably 80% or higher, more preferably 85% or higher, further preferably 90% or higher, even further preferably 93% or higher, still further preferably 95% or higher, and particularly preferably 98% or higher sequence identity. Most preferably, the polynucleotide has a nucleotide sequence identical to the nucleotide sequence of a target partial region. Sequence identity is defined in the same manner as the sequence identity of the amino acid sequence described above. Even if a terminus of a polynucleotide for cancer detection contains a region that does not hybridize thereto, in the case of a probe, it can be used for detection as long as a hybridizing region occupies about a half or more of the entire probe. In the case of a primer, it can be used for detection as long as a hybridizing region occupies about a half or more of the entire primer and is located on the 3' terminal side, since this allows a normal annealing and extension reaction to take place. When a terminus of a polynucleotide for cancer detection contains a non-hybridizing region, as described above, sequence identity with a target nucleotide sequence is calculated focusing only on the hybridizing region without taking a non-hybridizing region into consideration.

[0047] In the present invention, the term "partial sequence" (or "partial region") refers to a part of a nucleotide sequence represented by any of the odd-numbered SEQ ID NOs: 1 to 29. Specifically, the partial sequence comprises at least 15 to 19 continuous nucleotides, preferably 18 or more continuous nucleotides, more preferably at least 20 or 25 continuous nucleotides, and further preferably at least 30, 40, or 50 continuous nucleotides. The expression "the nucleotide sequence represented by SEQ ID NO: 5" used herein refers to, in addition to the nucleotide sequence actually shown in SEQ ID NO: 5, a sequence complementary thereto. Accordingly, the expression "a polynucleotide having the nucleotide sequence represented by SEQ ID NO: 5" refers to, for example, a single-stranded polynucleotide having the nucleotide sequence actually represented by SEQ ID NO: 5, a single-stranded polynucleotide having a nucleotide sequence complementary to the nucleotide sequence represented by SEQ ID NO: 5, or a double-stranded polynucleotide consisting of the two single-stranded polynucleotides. When a polynucleotide to be used in the present invention is prepared or a polynucleotide encoding a polypeptide to be used in the present invention is prepared, any of the nucleotide sequences is appropriately selected, and a person skilled in the art can readily perform such selection.

[0048] The number of nucleotides in a polynucleotide for cancer detection is preferably 18 or more in view of ensuring specificity. When the polynucleotide is used as a probe, it preferably comprises 18 or more nucleotides, and it further preferably comprises from 20 nucleotides to the full length of the coding region. When the polynucleotide is used as a primer, it preferably comprises 18 to 50 nucleotides. A preferable example of the polynucleotide for cancer detection is a polynucleotide comprising 18 or more continuous nucleotides in a nucleotide sequence represented by any of the odd-numbered SEQ ID NOs: 1 to 29.

[0049] It is apparent to a person skilled in the art who refers to the description of the present invention that: a polynucleotide specifically hybridizing to a partial region in SEQ ID NO: 5, 7, 9, 11, or 13 is used for measuring the amount of

a nucleic acid (e.g., mRNA or cDNA synthesized from mRNA) encoding the canine CAPRIN-1 protein of SEQ ID NO: 6, 8, 10, 12, or 14, respectively; and a polynucleotide specifically hybridizing to a partial region in SEQ ID NO: 1 or 3 is used for measuring the amount of a nucleic acid (e.g., mRNA or cDNA synthesized from mRNA) encoding the human CAPRIN-1 protein of SEQ ID NO: 2 or 4, respectively. However, a protein from a given mammal and a homolog thereof from another mammal generally share a high sequence identity even at the nucleotide sequence level. Thus, the sequence identity among the nucleotide sequences of SEQ ID NOs: 1 to 13 is also as high as 94% to 100%. Accordingly, a polynucleotide specifically hybridizing to a partial region of the sequence of SEQ ID NO: 5 can also specifically hybridize to a partial region corresponding to the partial region of any of the odd-numbered SEQ ID NOs: 1 to 29.

[0050] In fact, a pair of primers having the nucleotide sequences represented by SEQ ID NO: 33 and 34 specifically hybridize to both a partial region of any of the odd-numbered SEQ ID NOs: 1 to 29 and a partial region of the sequence of SEQ ID NO: 5, as described in the examples below. Thus, both mRNA encoding the canine CAPRIN-1 of SEQ ID NO: 6 and mRNA encoding a homolog thereof can be measured. With the use of a polynucleotide specifically hybridizing to a partial region of the sequence of SEQ ID NO: 5, accordingly, not only mRNA encoding the canine CAPRIN-1 of SEQ ID NO: 6 but also mRNA encoding the human CAPRIN-1 of SEQ ID NO: 2 or 4 can be measured. Similarly, mRNA encoding CAPRIN-1 of another mammal such as a cat can also be measured. When a polynucleotide for cancer detection is designed, it is more desirable to select partial regions having particularly high sequence identity from among the odd-numbered SEQ ID NOs: 1 to 29 (and identical nucleotide sequences are preferable). If there is a particularly high sequence identity having partial region between canine CAPRIN-1 and human CAPRIN-1, , a region showing very high sequence identity with such region is expected to be also present in a homolog gene of another animal species. Through selection of such a partial region, accuracy for measuring mRNA encoding CAPRIN-1 of an animal species other than dogs or humans can be increased.

[0051] A method for measuring a nucleic acid in test object using a polynucleotide specifically hybridizing to a partial region of the nucleic acid as a probe or a primer(s) for nucleic acid amplification method such as PCR is well known. Examples of such method include, in addition to RT-PCR as specifically described in the examples below, Northern blot and *in situ* hybridization. When the amount of mRNA is measured in the present invention, any such well-known measurement method can be employed.

[0052] A nucleic acid amplification method such as PCR is well known in the art, and reagent kits and apparatuses used therefor are commercially available, so that the method can be easily performed. Specifically, denaturation, annealing, and extension steps are each performed using a nucleic acid in test object (e.g., the cDNA of a gene encoding a protein having an amino acid sequence represented by any of the even-numbered SEQ ID NOs: 2 to 30) as a template and a pair of polynucleotides (primers) for cancer detection in a known buffer in the presence of thermostable DNA polymerase such as Taq polymerase or Pfu polymerase and dNTPs (here, N = A, T, C, and G) by varying the temperature of the reaction solution in each step. In general, the denaturation step is performed at 90°C to 95°C, the annealing step is performed at or near the Tm of the template and the primers (preferably within ± 4°C), and the extension step is performed at 72°C, which is the optimum temperature for thermostable DNA polymerase such as Taq polymerase or Pfu polymerase, or a temperature near the optimum temperature. The duration of each step is adequately set to between about 30 seconds and 2 minutes. This heating cycle is repeated about 25 to 40 times, for example, so that the template nucleic acid region sandwiched between a pair of primers is amplified. The nucleic acid amplification method is not limited to PCR, and any other nucleic acid amplification methods well known in the art can be employed. When a nucleic acid amplification method is performed using a pair of polynucleotides for cancer detection as primers and a nucleic acid in test object as a template, as described above, the nucleic acid is amplified. If a sample does not contain the test nucleic acid, however, amplification does not take place. Accordingly, an amplification product may be detected so as to determine the presence or absence of the nucleic acid in the sample. An amplification product can be detected by a method that comprises subjecting a reaction solution after amplification to electrophoresis and then staining the band with ethidium bromide or the like or a method that comprises immobilizing an amplification product after electrophoresis on a solid phase such as a nylon membrane, performing hybridization with a labeling probe that specifically hybridizes to a nucleic acid, washing, and then detecting the label. Also, so-called real-time detection PCR is performed using a quencher fluorescent dye and a reporter fluorescent dye, and the amount of a nucleic acid in a specimen can thus be quantified. Since kits for real-time detection PCR are commercially available, real-time detection PCR can be easily performed. Further, semi-quantitative measurement of a nucleic acid in test object can also be carried out based on electrophoresis band intensity. A nucleic acid in test object may be either mRNA or cDNA reversely transcribed from mRNA. When mRNA is amplified as a nucleic acid, a NASBA method (the 3SR method or TMA method) using the above pair of primers can also be employed. The NASBA method is well known, and kits therefor are also commercially available, so that the method can be easily performed using the above pair of primers.

[0053] As a probe, a labeled probe that is prepared by labeling a polynucleotide for cancer detection with a fluorescent label, a radiolabel, a biotin label, or the like can be used. Methods for labeling a polynucleotide are well known. The presence or absence of a nucleic acid in a sample can be examined by immobilizing a nucleic acid or an amplification product thereof, performing hybridization with a labeled probe, washing, and then measuring the label bound to the solid

phase. Alternatively, a polynucleotide for cancer detection is immobilized, a nucleic acid in test object is hybridized thereto, and the test nucleic acid bound to the solid phase can then be detected using the labeled probe or the like. In such a case, a polynucleotide for cancer detection bound to a solid phase is also referred to as a "probe." Methods for measuring a nucleic acid using a polynucleotide probe are also well known in the art. Such a method can be performed by, in a buffer, bringing a polynucleotide probe into contact with a nucleic acid in test object at Tm or near Tm (preferably, ± 4°C) for hybridization, washing, and then measuring the labeled probe hybridized or the template nucleic acid bound to the solid-phase probe. Examples of such method include well-known methods such as Northern blotting, *in situ* hybridization, and Southern blotting. In the present invention, any well-known method is applicable.

[0054] According to the detection method of the present invention, whether or not a subject animal (or a subject) is afflicted with pancreatic cancer is evaluated based on the presence or amount of CAPRIN-1 expression measured as described above. While pancreatic cancer can be detected only by measuring the presence or amount of CAPRIN-1 expression in a subject animal, it is preferable that the expression levels (the antibody level, polypeptide level, or mRNA level) of CAPRIN-1 in one or more samples of healthy subjects is examined and the determined value of a subject animal is compared with the standard value obtained from healthy subjects, in view of enhancing detection accuracy. To further enhance detection accuracy, CAPRIN-1 expression levels are measured for samples obtained from many patients found to have pancreatic cancer, so as to obtain a standard value for pancreatic cancer patients, and the determined value of a subject animal may then be compared with both the standard value for healthy subjects and the standard value for pancreatic cancer patients. The above standard values can be determined by, for example, quantifying the CAPRIN-1 expression level in each sample and calculating the mean value thereof. The standard value for healthy subjects and the same for pancreatic cancer patients can be determined in advance by measuring CAPRIN-1 expression levels in many healthy subjects and pancreatic cancer patients. When comparison with the standard value is performed in the method of the present invention, accordingly, a standard value determined in advance may be used.

[0055] The detection method of the present invention may comprise diagnosis based on other cancer antigens or cancer markers in combination. This can further enhance the accuracy of pancreatic cancer detection. When an antibody specifically existing in pancreatic cancer patients is measured by the method of the present invention, for example, another polypeptide that is often expressed in a cancer tissue can be used in combination as an antigen in a manner similar to that used for polypeptides described above. Also, the method of the present invention may be performed in combination with diagnosis using a previously known cancer marker.

[0056] Pancreatic cancer to be subjected to the method for detecting pancreatic cancer of the present invention is pancreatic cancer expressing CAPRIN-1. Examples of such cancer include, but are not limited to, pancreatic ductal carcinoma, invasive pancreatic ductal carcinoma, adenocarcinoma, acinar cell carcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), pancreatoblastoma, serous cystadenocarcinoma, solid-pseudopapillary tumor (SPT), gastrinomas (Zollinger-Ellison syndrome), glucagonomas, insulinomas, multiple endocrine neoplasia Type-1 (MEN1) (Wermer syndrome), nonfunctional islet cell tumor, somatostatinomas, and VIPomas. A subject in the method of the present invention is a mammal, preferably a human or a dog.

[0057] Examples of samples to be subjected to the method of the present invention include body fluids, such as blood, serum, blood plasma, ascites fluid, and pleural effusion, tissues, and cells. In the first method and the second method, in particular, serum, blood plasma, ascites fluid, pleural effusion, tissue, and cell samples can be preferably used. In the third method comprising measuring a nucleic acid such as mRNA, tissue and cell samples are preferable.

[0058] One or more polypeptides to be used as antigens for immunoassay in the first method described above (i.e., the canine CAPRIN-1 of SEQ ID NO: 2 and a homolog thereof, a specifically reactive partial polypeptide, a specifically reactive modified polypeptide, and a specifically reactive addition polypeptide) can be provided as reagents or kits for detection of pancreatic cancer. Such a reagent may consist of the above polypeptide, or it may contain various additives useful for stabilization of the polypeptide, a buffer necessary for assay, secondary antibodies, substrates for enzymes, or the like, separately. Alternatively, such a reagent can be immobilized on a solid phase such as a plate or membrane. Preferable examples of such polypeptides are given above.

[0059] An antibody or an antigen-binding fragment thereof, which undergoes an antigen-antibody reaction with CAPRIN-1, used for immunoassays of CAPRIN-1 by the second method can also be provided in the form of a reagent for pancreatic cancer detection. The reagent for pancreatic cancer detection may consist of the above antibody or an antigen-binding fragment thereof. The reagent may contain various additives useful for stabilization of such antibody or an antigen-binding fragment thereof. Alternatively, a metal, such as manganese or iron, may be bound to the antibody or an antigen-binding fragment thereof. When such metal-bound antibody or an antigen-binding fragment thereof is administered to a living organism, the metal-bound antibody or antigen-binding fragment thereof is accumulated at an increased level at a site at which the antigen protein is present at a higher level. When such metal-bound antibody or antigen-binding fragment thereof is administered to a living organism, the metal-bound antibody or antigen-binding fragment thereof is accumulated at an increased level at a site at which the antigen protein is present at a higher level. Therefore, the metal is measured by MRI or the like, and the presence of cancer cells producing the antigen protein can

be thus detected.

[0060] Furthermore, one or more the above polynucleotides for pancreatic cancer detection to be used for measuring a nucleic acid such as mRNA in the third method can also be provided as a reagent or kit for pancreatic cancer detection. In such a case, the reagent for pancreatic cancer detection may consist of the polynucleotide, or it may contain various additives useful for stabilization of the polypeptide, a buffer necessary for assay (e.g., a fluorescent label), and the like, separately. The polynucleotide for pancreatic cancer detection contained in the reagent is preferably a primer(s) or a probe(s). Conditions and preferable examples of the polynucleotide for pancreatic cancer detection are as described above.

Examples

[0061] The present invention will be described in more detail with reference to the following examples, although the technical scope of the present invention is not limited to the examples.

[Example 1] Obtaining pancreatic cancer antigenic protein by SEREX method (1) Construction of cDNA library

[0062] Total RNA was extracted from a testis tissue of a healthy dog by the acid guanidium-phenol-chloroform method, and poly A RNA was purified using an Oligotex-dT30 mRNA purification kit (Takara Shuzo, Co., Ltd.) in accordance with the protocols attached to the kit.

[0063] A canine testis cDNA phage library was synthesized using the thus obtained mRNA (5 μg). The cDNA phage library was constructed using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA GigapackIII Gold Cloning Kit (STRATAGENE) in accordance with the protocols attached to the kits. The size of the thus constructed cDNA phage library was 7.73 x 10^5 pfu/ml.

(2) Screening of cDNA library using serum

[0064] Immunoscreening was performed using the canine testis cDNA phage library constructed above. Specifically, host *Escherichia coli* (XL1-Blue MRF') was infected with the phage on an NZY agarose plate (Φ90 x 15 mm) so as to obtain 2,210 clones. *E. coli* cells were cultured at 42°C for 3 to 4 hours to form plaques. The plate was covered with a nitrocellulose membrane (Hybond C Extra: GE Healthcare Bio-Science) impregnated with IPTG (isopropyl-β-D-thiogalactoside) at 37°C for 4 hours, so that the protein was induced to express and then transferred to the membrane. Thereafter, the membrane was collected and then soaked in TBS (10 mM Tris-HCl, 150 mM NaCl, pH 7.5) containing 0.5% powdered skim milk, followed by shaking at 4°C overnight, so as to suppress nonspecific reactions. The filter was subjected to a reaction with a 500-fold diluted serum of a afflicted dog r at room temperature for 2 to 3 hours.

[0065] As the above serum of the afflicted dog, a serum collected from a canine afflicted with pancreatic cancer was used. The serum was stored at -80°C and then subjected to pre-treatment immediately before use. A method for serum pretreatment is as follows. Specifically, host *Escherichia coli* (XL1-Blue MRF') was infected with a λ ZAP Express phage into which no foreign gene had been inserted, and culture was conducted overnight on a NZY plate medium at 37°C. Subsequently, buffer (0.2 M $NAHCO_3$, pH 8.3) containing 0.5 M NaCl was added to the plate, the plate was allowed to stand at 4°C for 15 hours, and a supernatant was then collected as an *Escherichia coli*/phage extract. The thus collected *Escherichia coli*/phage extract was then applied to an NHS-column (GE Healthcare Bio-Science), so that an Escherichia coli/phage-derived protein was immobilized. The serum of the afflicted dog was applied to the protein-immobilized column for reaction and *Escherichia coli* and an antibody adsorbed to the phage were then removed from the serum. The serum fraction that had passed through the column was diluted 500-fold with TBS containing 0.5% powdered skim milk. The diluted serum fraction was used as an immunoscreening material.

[0066] A membrane onto which the treated serum and the above fusion protein had been blotted was washed 4 times with TBS-T (0.05% Tween 20/TBS), and the membrane was then allowed to react with goat anti-canine IgG (Goat anti-Dog IgG-h+l HRP conjugated, BETHYL Laboratories) diluted 5000-fold with TBS containing 0.5% powdered skim milk as a secondary antibody at room temperature for 1 hour. Detection was performed via an enzymatic color development reaction using the NBT/BCIP reaction solution (Roche). Colonies that matched sites positive for the color development reaction were collected from the NZY agarose plate (Φ90 x 15 mm) and then dissolved in 500 μl of an SM buffer (100 mM NaCl, 10 mM $MgClSO_4$, 50 mM Tris-HCl, 0.01% gelatin, pH 7.5). Until colonies positive for color development reaction were unified, secondary screening and tertiary screening were repeated by a method similar to the above, so that 30,940 phage clones reacting with the serum IgG were screened. Thus, 5 positive clones were isolated.

(3) Homology search for isolated antigen gene

[0067] For nucleotide sequence analysis of the 5 positive clones isolated by the above method, a procedure for

conversion from phage vectors to plasmid vectors was performed. Specifically, 200 μl of a solution containing host *Escherichia coli* (XL1-Blue MRF') at the absorbance (OD 600) of 1.0 was prepared. The solution was mixed with 250 μl of a purified phage solution and 1 μl of ExAssist helper phage (STRATAGENE), the mixture was subjected to a reaction at 37°C for 15 minutes, 3 ml of LB medium was added thereto, and culture was then performed at 37°C for 2.5 to 3 hours. Immediately thereafter, the temperature of the solution was kept in a water bath at 70°C for 20 minutes, centrifugation was performed at 4°C and 1000 x g for 15 minutes, and the supernatant was then collected as a phagemid solution. Subsequently, 200 μl of a solution containing phagemid host *Escherichia coli* (SOLR) at the absorbance OD_{600} of 1.0 was prepared. The resulting solution was mixed with 10 μl of a purified phage solution, followed by a reaction at 37°C for 15 minutes. The reaction product (50 ml) was seeded on LB agar medium containing ampicillin (final concentration: 50 μg/ml), and culture was conducted at 37°C overnight. Transformed SOLR single colony was collected and then cultured in LB medium containing ampicillin (final concentration: 50 μg/ml) at 37°C. Thereafter, plasmid DNA containing an insert of interest was purified using the QIAGEN plasmid Miniprep Kit (QIAGEN).

[0068] The purified plasmid was subjected to analysis of the full-length insert sequence by the primer walking method using the T3 primer represented by SEQ ID NO: 31 and the T7 primer represented by SEQ ID NO: 32. As a result of sequence analysis, the gene sequences represented by SEQ ID NOs: 5, 7, 9, 11, and 13 were obtained. A homology search program, BLAST search (http://www.ncbi.nlm.nih.gov/BLAST/), was performed using the nucleotide sequences and amino acid sequences (SEQ ID NOs: 6, 8, 10, 12, and 14) of the genes. As a result of this homology search with known genes, all of the 5 obtained genes were found to encode CAPRIN-1. The sequence identity among the 5 genes was 100% for nucleotide sequence and 99% for amino acid sequence in regions translated into proteins. Also, the sequence identity between the canine gene (any of SEQ ID NO: 5, 7, 9, 11, or 13) and a gene encoding a human homolog thereof was 94%for nucleotide sequence and 98% for amino acid sequence in regions translated into proteins. The nucleotide sequences of the human homolog are represented by SEQ ID NOs: 1 and 3 and the amino acid sequences of the same are represented by SEQ ID NOs: 2 and 4. Also, the sequence identity between the obtained canine gene and a gene encoding a cattle homolog was 94% for nucleotide sequence and 97% for amino acid sequence in regions translated into proteins. The nucleotide sequence of the cattle homolog is represented by SEQ ID NO: 15 and the amino acid sequence of the same is represented by SEQ ID NO: 16. The sequence identity between the gene encoding the human homolog and the gene encoding the cattle homolog was 94% for nucleotide sequences and ranged from 93% to 97% for amino acid sequence in regions translated into proteins. Also, the sequence identity between the obtained canine gene and a gene encoding an equine homolog was 93% for nucleotide sequence and 97% for amino acid sequence in regions translated into proteins. The nucleotide sequence of the equine homolog is represented by SEQ ID NO: 17 and the amino acid sequence of the same is represented by SEQ ID NO: 18. The sequence identity between the gene encoding the human homolog and the gene encoding the equine homolog was 93% for nucleotide sequence and 96% for amino acid sequence in regions translated into proteins. Also, the sequence identity between the obtained canine gene and a gene encoding the mouse homolog ranged from 87% to 89% in terms of nucleotide sequence and ranged from 95% to 97% for amino acid sequence in regions translated into proteins. The nucleotide sequences of the mouse homolog are represented by SEQ ID NOs: 19, 21, 23, 25, and 27 and the amino acid sequences of the same are represented by SEQ ID NOs: 20, 22, 24, 26, and 28. The sequence identity between the gene encoding the human homolog and the gene encoding the mouse homolog ranged from 89% to 91% for nucleotide sequence and ranged from 95% to 96% for amino acid sequence in regions translated into proteins. Also, the sequence identity between the obtained canine gene and a gene encoding a chicken homolog was 82% for nucleotide sequence and 87% for amino acid sequence in regions translated into proteins. The nucleotide sequence of the chicken homolog is represented by SEQ ID NO: 29 and the amino acid sequence of the same is represented by SEQ ID NO: 30. The sequence identity between the gene encoding the human homolog and the gene encoding the chicken homolog ranged from 81% to 82% for nucleotide sequence and 86% for amino acid sequence in regions translated into proteins.

(4) Gene expression analysis in human pancreatic cancer cell lines

[0069] Expression of the genes obtained by the above method in human normal tissues (i.e., mammary gland, brain, bone marrow, lung, esophagus, pancreas, and testis) and 4 types of pancreatic cancer cell lines (i.e., Capan-2, MIAPaCa-2, PANC-1, and BxPC-3) was examined by RT-PCR (reverse transcription-PCR). A reverse transcription reaction was performed as follows. Specifically, total RNA was extracted from each tissue (50 mg to 100 mg) and each cell line (5-10 x 10^6 cells) using the TRIZOL reagent (Invitrogen) in accordance with the attached protocols. cDNA was synthesized using the total RNA and the Superscript First-Strand Synthesis System for RT-PCR (Invitrogen) in accordance with the attached protocols. PCR was performed as follows using primers specific to the obtained genes (represented by SEQ ID NOs: 33 and 34). Specifically, PCR was performed by preparing a reaction solution to bring a total amount thereof to 25 μl with the addition of reagents and an included buffer (i.e., 0.25 μl of a sample prepared by reverse transcription reaction, the above primers (2 μM each), dNTPs (0.2 mM each), 0.65 U of ExTaq polymerase (Takara Shuzo, Co., Ltd.)), the resulting solution was subjected to a cycle of 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30

seconds using a Thermal Cycler (BIO RAD), and this cycle was repeated 30 times. The gene-specific primers mentioned above were used to amplify the region between the nucleotide No. 698 and the nucleotide No. 1124 in the nucleotide sequence represented by SEQ ID NO: 1 (the human CAPRIN-1 gene). For comparison, GAPDH-specific primers (represented by SEQ ID NOs: 35 and 36) were used at the same time. As a result of inspection of human CAPRIN-1 gene expression, expression thereof was observed only in the testis in the case of healthy canine tissues, although expression was observed in the pancreatic cancer cells. The results demonstrate that CAPRIN-1 expression was not observed in normal tissues other than those of the testis, while CAPRIN-1 expression was observed in the pancreatic cancer cells.

(5) CAPRIN-1 expression in normal mouse and canine tissues

[0070] Mice (Balb/c, female) and dogs (beagle dogs, female) were exsanguinated under ether anesthesia and ketamine/isoflurane anesthesia. After laparotomy, organs (stomach, liver, eyeball, thymus gland, muscle, bone marrow, uterus, small intestine, esophagus, heart, kidney, salivary gland, large intestine, mammary gland, brain, lung, skin, adrenal gland, ovary, pancreas, spleen, and bladder) were each transferred to a 10 cm dish containing PBS. Each organ was cut open in PBS and then fixed by perfusion overnight with 0.1 M phosphate buffer (pH 7.4) containing 4% paraformaldehyde (PFA). The perfusate was discarded, the tissue surface of each organ was rinsed with PBS, and a PBS solution containing 10% sucrose was then introduced into a 50 ml centrifugal tube. Each tissue was then introduced into each tube, followed by shaking using a rotor at 4°C for 2 hours. Each solution was substituted with a PBS solution containing 20% sucrose and then allowed to stand at 4°C until tissues precipitated. Each solution was substituted with a PBS solution containing 30% sucrose and then allowed to stand at 4°C until tissues precipitated. Each tissue was removed and a necessary portion was excised with a surgical scalpel. Subsequently, the OCT compound (Tissue Tek) was applied and spread over each tissue surface, and the tissues were then placed on Cryomold. Cryomold was placed on dry ice for rapid freezing. Tissues were sliced into pieces of 10 to 20 μm long using a cryostat (LEICA), the sliced tissue pieces were then air-dried on glass slides for 30 minutes using a hair dryer, and glass slides onto which sliced tissue pieces had been applied were thus prepared. Subsequently, each glass slide was introduced into a staining bottle filled with PBS-T (saline containing 0.05% Tween 20), a procedure involving exchanging PBS-T with fresh PBS-T was performed every 5 minutes, and this procedure was repeated 3 times. Excess water around each specimen was removed using Kimwipes and each section was then encircled using DAKOPEN (DAKO). As blocking solutions, a MOM mouse Ig blocking reagent (VECTASTAIN) was applied onto mouse tissue and a PBS-T solution containing a 10% fetal calf serum was applied onto canine tissue. The resultants were allowed to stand in a moist chamber at room temperature for 1 hour. Subsequently, a solution prepared with the blocking solution to a 10 μg/ml anti-CAPRIN-1 monoclonal antibody (monoclonal antibody #8) having the heavy chain variable region of SEQ ID NO: 55 and the light chain variable region of SEQ ID NO: 56, which reacts with the cancer cell surfaces prepared in Example 3, was applied onto each slide glass and then allowed to stand within a moist chamber at 4°C overnight. After 3 instances of 10-minutes-washing with PBS-T, a MOM biotin-labeled anti-IgG antibody (VECTASTAIN) diluted 250-fold with the blocking solution was applied onto each glass slide and then allowed to stand within a moist chamber at room temperature for 1 hour. After 3 instances of 10-minutes-washing with PBS-T, an avidin-biotin ABC reagent (VECTASTAIN) was applied and then allowed to stand within a moist chamber at room temperature for 5 minutes. After 3times of 10-minutes-washing with PBS-T, a DAB staining solution (10 mg of DAB + 10 μl of 30% H_2O_2, and 50 ml of 0.05M Tris-HCl, pH 7.6) was applied, and the glass slides were then allowed to stand within a moist chamber at room temperature for 30 minutes. Glass slides were rinsed with distilled water and a hematoxylin reagent (DAKO) was then applied. After being allowed to stand at room temperature for 1 minute, the glass slides were rinsed with distilled water. The glass slides were put in 70%, 80%, 90%, 95%, and 100% ethanol solutions in such order for 1 minute each and then allowed to stand in xylene overnight. The glass slides were removed, coverslipped with Glycergel Mounting Medium (DAKO), and then observed. As a result, CAPRIN-1 expression was observed to a slight degree within cells in all of salivary gland, kidney, colon, and stomach tissues, but no CAPRIN-1 expression was observed on cell surfaces. Also, absolutely no CAPRIN-1 expression was observed in tissues from other organs.

[Example 2] Preparation of canine and human CAPRIN-1 proteins

(1) Preparation of recombinant protein

[0071] A recombinant protein was prepared by the following method based on the gene of SEQ ID NO: 5 obtained in Example 1. PCR was performed by preparing a reaction solution to bring a total amount thereof to 50 μl with the addition of reagents and an included buffer (i.e., 1 μl of a vector prepared from the phagemid solution obtained in Example 1 and then subjected to sequence analysis, 2 types of primers containing NdeI and KpnI restriction enzyme cleavage sequences (0.4 μM each; SEQ ID NOs: 37 and 38), 0.2 mM dNTPs, and 1.25 U PrimeSTAR HS polymerase (Takara Shuzo, Co., Ltd.)), the resulting reaction solution was subjected to a cycle of 98°C for 10 seconds and 68°C for 1.5

minutes using a Thermal Cycler (BIO RAD), and this cycle was repeated 30 times. The above 2 types of primers were used to amplify the region encoding the full-length amino acid sequence of SEQ ID NO: 6 (canine CAPRIN-1). After PCR, the amplified DNA was subjected to 1% agarose gel electrophoresis, and a DNA fragment of about 1.4 kbp was then purified from the gel using a QIAquick Gel Extraction Kit (QIAGEN).

[0072] The purified DNA fragment was ligated to a pCR-Blunt cloning vector (Invitrogen). The vector was transformed into *Escherichia coli,* the plasmid was collected, and the amplified gene fragment was confirmed to match the target sequence via sequencing. The plasmid that matched the target sequence was treated with NdeI and KpnI restriction enzymes, the resultant was purified using a QIAquick Gel Extraction Kit, and the target gene sequence was inserted into a pET30b expression vector (Novagen) for *Escherichia coli* treated with NdeI and KpnI restriction enzymes. With the use of the resulting vector, a His tag-fused recombinant protein can be produced. The plasmid was transformed into *Escherichia coli* BL21 (DE3) for expression, and the target protein was induced to express in *Escherichia coli* with the aid of 1 mM IPTG.

[0073] Separately, the recombinant protein of a canine homolog gene was prepared by the following method based on the gene of SEQ ID NO: 7. PCR was performed by preparing a reaction solution to bring a total amount thereof to 50 μl with the addition of reagents and an included buffer (i.e., 1 μl of cDNA, the expression of which was confirmed via RT-PCR, selected from among the various tissues and cellular cDNAs prepared in Example 1, 2 types of primers containing NdeI and KpnI restriction enzyme cleavage sequences (0.4 μM each; SEQ ID NOs: 39 and 40), 0.2 mM dNTPs, and 1.25 U PrimeSTAR HS polymerase (Takara Shuzo, Co., Ltd.)), the resulting reaction solution was subjected to a cycle of 98°C for 10 seconds and 68°C for 2.5 minutes using a Thermal Cycler (BIO RAD), and this cycle was repeated 30 times. The above 2 types of primers were used to amplify the region encoding the full-length amino acid sequence of SEQ ID NO: 8. After PCR, the amplified DNA was subjected to 1% agarose gel electrophoresis, and a DNA fragment of about 2.2 kbp was then purified from the gel using a QIAquick Gel Extraction Kit (QIAGEN).

[0074] The purified DNA fragment was ligated to a pCR-Blunt cloning vector (Invitrogen). The vector was transformed into *Escherichia coli,* the plasmid was collected, and the amplified gene fragment was confirmed to match the target sequence via sequencing. The plasmid that matched the target sequence was treated with NdeI and KpnI restriction enzymes, the resultant was purified using a QIAquick Gel Extraction Kit, and the target gene sequence was inserted into a pET30b expression vector (Novagen) for *Escherichia coli* treated with NdeI and KpnI restriction enzymes. With the use of the resulting vector, a His tag-fused recombinant protein can be produced. The plasmid was transformed into *Escherichia coli* BL21 (DE3) for expression, and the target protein was induced to express in *Escherichia coli* with the aid of 1 mM IPTG.

[0075] Separately, the recombinant protein of a human homolog gene was prepared by the following method based on the gene of SEQ ID NO: 1. PCR was performed by preparing a reaction solution to bring a total amount thereof to 50 μl with the addition of reagents and an included buffer (i.e., 1 μl of cDNA, the expression of which was confirmed via RT-PCR, selected from among the various tissue and cellular cDNAs prepared in Example 1, 2 types of primers containing SacI and XhoI restriction enzyme cleavage sequences (0.4 μM each; SEQ ID NOs: 41 and 42), 0.2 mM dNTPs, and 1.25 U PrimeSTAR HS polymerase (Takara Shuzo, Co., Ltd.)), the resulting reaction solution was subjected to a cycle of 98°C for 10 seconds and 68°C for 2.5 minutes using a Thermal Cycler (BIO RAD), and this cycle was repeated 30 times. The above 2 types of primers were used to amplify the region encoding the full-length amino acid sequence of SEQ ID NO: 2. After PCR, the amplified DNA was subjected to 1% agarose gel electrophoresis, and a DNA fragment of about 2.1 kbp was then purified from the gel using a QIAquick Gel Extraction Kit (QIAGEN).

[0076] The purified DNA fragment was ligated to a pCR-Blunt cloning vector (Invitrogen). The vector was transformed into *Escherichia coli,* the plasmid was collected, and the amplified gene fragment was confirmed to match the target sequence via sequencing. The plasmid that matched the target sequence was treated with SacI and XhoI restriction enzymes, the resultant was purified using a QIAquick Gel Extraction Kit, and the target gene sequence was inserted into a pET30a expression vector (Novagen) for *Escherichia coli* treated with SacI and XhoI restriction enzymes. With the use of the resulting vector, a His tag-fused recombinant protein can be produced. The plasmid was transformed into *Escherichia coli* BL21 (DE3) for expression, and the target protein was induced to express in *Escherichia coli* with the aid of 1 mM IPTG.

(2) Purification of recombinant protein

[0077] The above-obtained recombinant *Escherichia coli* strain expressing SEQ ID NO: 1, 5, or 7 was cultured at 37°C in LB medium containing 30 μg/ml kanamycin until the absorbance at 600 nm reached around 0.7. Thereafter, isopropyl-β-D-1-thiogalactopyranoside was added to a final concentration of 1 mM, and culture was conducted at 37°C for 4 hours. Subsequently, the culture was centrifuged at 4800 rpm for 10 minutes to collect cells. The cell pellet was suspended in phosphate buffered saline and then centrifuged at 4800 rpm for 10 minutes to wash the cells.

[0078] The cells were suspended in phosphate buffered saline and then subjected to ultrasonication on ice. The ultrasonicated *Escherichia coli* solution was centrifuged at 6000 rpm for 20 minutes, the resulting supernatant was

designated as a soluble fraction, and the resulting precipitate was designated as an insoluble fraction.

[0079] The soluble fraction was added to a nickel chelate column (carrier: Chelating Sepharose™ Fast Flow (GE Healthcare), column capacity: 5 ml, 50 mM hydrochloric acid buffer (pH 8.0) as equilibrating buffer)) prepared in accordance with a conventional method. The non-adsorbed fraction was washed with 10 column volumes of 50 mM hydrochloric acid buffer (pH 8.0) and 20 mM phosphate buffer (pH 8.0) containing 20 mM imidazole. Immediately thereafter, 6 beds were eluted with 20 mM phosphate buffer (pH 8.0) containing 100 mM imidazole. After the elution of the protein of interest had been confirmed by Coomassie staining, an elution fraction of 20 mM phosphate buffer (pH 8.0) containing 100 mM imidazole was added to a strong anion exchange column (carrier: Q Sepharose™ Fast Flow (GE Healthcare), column volume: 5 ml, and 20 mM phosphate buffer (pH 8.0) as equilibrating buffer). The non-adsorbed fraction was washed with 10 column volumes of 20 mM phosphate buffer (pH 7.0) and 20 mM phosphate buffer (pH 7.0) containing 200 mM sodium chloride. Immediately thereafter, 5 beds were eluted using 20 mM phosphate buffer (pH 7.0) containing 400 mM sodium chloride. Thus, purified fractions of proteins having the amino acid sequences represented by SEQ ID NO: 2, 6, and 8 were obtained, and these purified fractions were hereafter used as materials for administration tests.

[0080] Each of the purified preparations obtained by the above method (200 μl each) was dispensed into 1 ml of a reaction buffer (20 mM Tris-HCl, 50 mM NaCl, 2 mM $CaCl_2$, pH 7.4), and 2 μl of enterokinase (Novagen) was then added. The preparation was allowed to stand at room temperature overnight for reaction, a His tag was cleaved, and purification was then performed in accordance with the protocols attached to the Enterokinase Cleavage Capture Kit (Novagen). Subsequently, 1.2 ml of the purified preparation obtained by the above method was substituted with physiological phosphate buffer (Nissui Pharmaceutical Co., Ltd.) using ultrafiltration NANOSEP 10K OMEGA (PALL). Sterilized filtration was performed using 0.22 μm HT Tuffryn Acrodisc (PALL), and the resultants were used for the following experiments.

[Example 3] Preparation of antibody against CAPRIN-1

(1) Preparation of polyclonal antibody against CAPRIN-1-derived peptide

[0081] In order to obtain an antibody binding to CAPRIN-1, a CAPRIN-1-derived peptide (Arg-Asn-Leu-Glu-Lys-Lys-Lys-Gly-Lys-Leu-Asp-Asp-Tyr-Gln; SEQ ID NO: 43) was synthesized. The peptide as an antigen (1 mg) was mixed with the equivalent volume of an incomplete Freund's adjuvant (IFA) solution, and the mixture was subcutaneously administered to a rabbit 4 times every 2 weeks. Thereafter, blood was collected, and an antiserum containing a polyclonal antibody was obtained. Further, the antiserum was purified using a protein G carrier (GE Healthcare Bio-Sciences), and a polyclonal antibody against the CAPRIN-1-derived peptide was then obtained. Subsequently, the reactivity of the resulting polyclonal antibody to CAPRIN-1 on the cancer cell surface was examined using breast cancer cells. Specifically, 10^6 cells of the human breast cancer cell line MDA-MB-231 V were subjected to centrifugation in a 1.5 ml microcentrifugal tube, a PBS solution supplemented with 0.1% fetal bovine serum (FBS) containing the polyclonal antibody was added thereto, and the resultant was then allowed to stand on ice for 1 hour. After washing with PBS, an FITC-labeled goat anti-mouse IgG antibody (Invitrogen) diluted 500-fold with PBS containing 0.1% FBS was added to the solution, and the solution was then allowed to stand on ice for 1 hour. After washing with PBS, fluorescence intensity was measured using a FACS Calibur (Becton, Dickinson and Company). Separately, a control was prepared in accordance with a procedure similar to the above, except that PBS containing 0.1% FBS was added instead of the polyclonal antibody. As a result, fluorescence intensity in cells treated with the polyclonal antibody was found to be stronger than that in control cells, and the obtained polyclonal antibody was thus found to bind to the breast cancer cell surface.

(2) Preparation of monoclonal antibody against CAPRIN-1 protein

[0082] The antigenic protein (human CAPRIN-1) (100 μg) represented by SEQ ID NO: 2 prepared in Example 2 was mixed with the equivalent amount of a MPL+TDM adjuvant (Sigma), and the mixture was used as an antigen solution per mouse. The antigen solution was administered intraperitoneally to a 6-week-old Balb/c mouse (Japan SLC Inc.) and further administered 3 times every week. The spleen was removed 3 days after the final immunization, ground in between two sterilized glass slides, washed with PBS (-) (Nissui), and then centrifuged at 1500 rpm for 10 minutes to remove supernatants. This procedure was repeated 3 times to obtain spleen cells. The thus obtained spleen cells were mixed with the mouse myeloma SP2/0 cells (purchased from ATCC) at a ratio of 10:1. The PEG solution prepared by mixing 200 μl of RPMI1640 medium containing 10% FBS heated to 37°C and 800 μl of PEG1500 (Boehringer) was added to the cells. The solution was allowed to stand for 5 minutes for cell fusion. Centrifugation was performed at 1700 rpm for 5 minutes to remove supernatants, the cells were suspended in 150 ml of RPMI1640 medium (HAT selective medium) containing 15% FBS supplemented with 2% equivalent of HAT solution (Gibco), and the suspension was then seeded onto fifteen 96-well plates (Nunc) at 100 μl/well. Cells were cultured for 7 days at 37°C in the presence of 5% CO_2. Thus, hybridomas resulting from fusion of spleen cells with myeloma cells were obtained.

[0083] Hybridomas were selected using, as an indicator, the binding affinity of the antibody produced by the prepared hybridomas for the CAPRIN-1 protein. The CAPRIN-1 protein solution (1 μg/ml) prepared in Example 2 was added to a 96-well plate at 100 μl/well, and the resultant was allowed to stand at 4°C for 18 hours. Each well was washed 3 times with PBS-T, a 0.5% bovine serum albumin (BSA) solution (Sigma) was added at 400 μl/well, and the plate was then allowed to stand at room temperature for 3 hours. The solution was removed and each well was washed 3 times with 400 μl of PBS-T. Thereafter, each culture supernatant of the hybridomas obtained above was added at 100 μl/well, and the resultant was then allowed to stand at room temperature for 2 hours. Each well was washed 3 times with PBS-T, an HRP-labeled anti-mouse IgG (H+L) antibody (Invitrogen) diluted 5000-fold with PBS was added thereto at 100 μl/well, and the resultant was allowed to stand at room temperature for 1 hour. After each well was washed 3 times with PBS-T, a TMB substrate solution (Thermo) was added at 100 μl per/well, and the resultant was allowed to stand for 15 to 30 minutes, so as to allow the color to develop. Thereafter, 1N sulfuric acid was added at 100 μl/well to terminate the reaction. The absorbance was measured at 450 nm and 595 nm using a spectrophotometer. As a result, a plurality of hybridomas producing antibodies exhibiting high absorbance values were selected.

[0084] The thus selected hybridomas were added to a 96-well plate at 0.5 hybridomas per well and then cultured. After 1 week, hybridomas forming single colonies in wells were observed. Cells in these wells were further cultured, and hybridomas were selected using, as an indicator, the binding affinity of the antibody produced by the cloned hybridomas for the CAPRIN-1 protein. The CAPRIN-1 protein solution (1 μg/ml) prepared in Example 2 was added to a 96-well plate at 100 μl/well, and the resultant was allowed to stand at 4°C for 18 hours. Each well was washed 3 times with PBS-T, a 0.5% BSA solution was added at 400 μl/well, and the plate was then allowed to stand at room temperature for 3 hours. The solution was removed and each well was washed 3 times with 400 μl of PBS-T. Thereafter, each culture supernatant of the hybridomas obtained above was added at 100 μl/well, and the resultant was then allowed to stand at room temperature for 2 hours. Each well was washed 3 times with PBS-T, an HRP-labeled anti-mouse IgG (H+L) antibody (Invitrogen) diluted 5000-fold with PBS was added thereto at 100 μl/well, and the resultant was allowed to stand at room temperature for 1 hour. After each well was washed 3 times with PBS-T, a TMB substrate solution (Thermo) was added at 100 μl per/well and then allowed to stand for 15 to 30 minutes, so as to allow the color to develop. Thereafter, 1N sulfuric acid was added at 100 μl/well to terminate the reaction, and the absorbance was measured at 450 nm and 595 nm using a spectrophotometer. As a result, a plurality of hybridomas producing monoclonal antibodies exhibiting reactivity to the CAPRIN-1 protein were selected, the culture supernatant of hybridomas was purified using a protein G carrier, and 150 monoclonal antibodies binding to the CAPRIN-1 protein were obtained.

[0085] Subsequently, monoclonal antibodies exhibiting reactivity to the surfaces of cancer cells expressing CAPRIN-1 were selected from among these monoclonal antibodies using breast cancer cells. Specifically, 10^6 cells of the human breast cancer cell line MDA-MB-231 V were subjected to centrifugation in a 1.5 ml microcentrifugal tube, 100 μl of the culture supernatant of the hybridomas was added thereto, and the resultant was then allowed to stand on ice for 1 hour. After washing with PBS, an FITC-labeled goat anti-mouse IgG antibody (Invitrogen) diluted 500-fold with PBS containing 0.1% FBS was added to the solution, and the solution was then allowed to stand on ice for 1 hour. After washing with PBS, fluorescence intensity was measured using a FACS Calibur (Becton, Dickinson and Company). Separately, a control was prepared in accordance with a procedure similar to the above, except that a medium was added instead of the antibody. As a result, 10 monoclonal antibodies exhibiting stronger fluorescence intensity than that of the control; i.e., 10 monoclonal antibodies exhibiting reactivity to the surfaces of breast cancer cells (#1 to #10), were selected. The heavy chain variable regions and the light chain variable regions of these monoclonal antibodies are shown in SEQ ID NOs: 44 to 60. The above 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.

(3) Identification of peptides in CAPRIN-1 protein to which antibodies against CAPRIN-1 reacting with breast cancer cell surface bind

[0086] With the use of monoclonal antibodies #1 to #10 against CAPRIN-1 reacting with the surfaces of breast cancer

cells obtained above, partial sequences in the CAPRIN-1 protein recognized by these monoclonal antibodies were identified.

[0087] To 100 μl of a recombinant CAPRIN-1 protein solution adjusted to a concentration of 1 μg/μl with PBS, first of all, DTT (Fluka) was added to result in a final concentration of 10 mM therein, and a reaction was allowed to proceed at 95°C for 5 minutes, so as to reduce disulfide bonds within the CAPRIN-1 protein. Subsequently, iodoacetamide (final concentration: 20 mM; Wako Pure Chemical Industries, Ltd.) was added, and thiol groups were subjected to alkylation at 37°C for 30 minutes under shaded conditions. The monoclonal antibodies #1 to #10 against CAPRIN-1 (50 μg each) were added to 40 μg of the reduced-alkylated CAPRIN-1 protein, the volume of the mixture was adjusted to 1 ml with 20 mM phosphate buffer (pH7.0), and the reaction was allowed to proceed at 4°C overnight with stirring and mixing.

[0088] Subsequently, trypsin (Promega) was added to a final concentration of 0.2 μg. After the reaction was allowed to proceed at 37°C for 1 hour, 2 hours, 4 hours, and then 12 hours, the resultants were mixed with protein A-glass beads (GE), which had been subjected to blocking with PBS containing 1% BSA (Sigma) and washing with PBS in advance, in 1 mM calcium carbonate and NP-40 buffer (20 mM phosphate buffer (pH 7.4), 5 mM EDTA, 150 mM NaCl, and 1% NP-40), and the reaction was allowed to further proceed for 30 minutes.

[0089] The reaction solutions were each washed with 25 mM ammonium carbonate buffer (pH 8.0), antigen-antibody complexes were then eluted using 100 μl of 0.1 % formic acid, and the eluates were subjected to LC-MS analysis using Q-TOF Premier (Waters-MicroMass) in accordance with the protocols attached to the instrument.

[0090] As a result, the polypeptide of SEQ ID NO: 61 was identified as a partial sequence of CAPRIN-1, which was recognized by all of the monoclonal antibodies #1 to #10 against CAPRIN-1. Further, the peptide of SEQ ID NO: 62 was identified as a partial sequence in the polypeptide of SEQ ID NO: 61 above, which was recognized by the monoclonal antibodies #1 to #4, #5 to #7, and #9. In addition, the monoclonal antibodies #1 to #4 were found to recognize the peptide of SEQ ID NO: 63, which was a partial peptide sequence thereof.

[Example 4] Diagnosis of pancreatic cancer using CAPRIN-1 polypeptide

1) Diagnosis of canine pancreatic cancer

[0091] As a result of pathological diagnosis using the removed tumor tissue samples, blood samples were collected from afflicted dogs confirmed to have malignant pancreatic ductal carcinoma, and sera were separated. With the use of the canine CAPRIN-1 protein (SEQ ID NO: 8) prepared in Example 2 and the anti-canine IgG antibody, the titer of the serum IgG antibody specifically reacting with the canine CAPRIN-1 protein was measured by an ELISA method.

[0092] The prepared canine CAPRIN-1 protein was immobilized by adding a recombinant protein solution diluted to 5 μg/ml with phosphate buffered saline to a 96-well immobilizer amino plate (Nunc) at 100 μl/well and then allowing the plate to stand at 4°C overnight. Blocking was performed by adding a 50 mM sodium bicarbonate buffer solution (pH 8.4) (hereafter, referred to as a "blocking solution") containing 0.5% BSA (bovine serum albumin, Sigma Aldrich Japan) at 100 μl/well, followed by shaking at room temperature for 1 hour. Serum diluted 1000-fold with the blocking solution was added at 100 μl/well and the mixture was then subjected to a reaction via shaking at room temperature for 3 hours. The reaction product was washed 3 times with phosphate buffered saline containing 0.05% Tween 20 (Wako Pure Chemical Industries, Ltd.; this solution is referred to as "PBS-T" herein), an HRP-modified canine IgG antibody (Goat anti-Dog IgG-h+l HRP conjugated: BETHYL Laboratories) diluted 3000-fold with the blocking solution was added at 100 μl/well, and the mixture was subjected to a reaction via shaking at room temperature for 1 hour. After the reaction product was washed 3 times with PBS-T, HRP substrate TMB (1-Step Turbo TMB (tetramethylbenzidine), PIERCE) was added at 100 μl/well, and an enzyme-substrate reaction was then conducted at room temperature for 30 minutes. Thereafter, a 0.5 M sulfuric acid solution (Sigma Aldrich Japan) was added at 100 μl/well to terminate the reaction, and the absorbance at 450 nm was measured using a microplate reader. As controls, a specimen onto which no recombinant protein prepared had been immobilized and a specimen to which the serum of a cancer-bearing dog would not be allowed to react were subjected to the treatment and comparison in the same manner as described above.

[0093] As a result, the titer of the antibody against a canine CAPRIN-1 protein of the sera derived from cancer-carrying dogs was found to be higher than that of the controls.

(2) Diagnosis of canine pancreatic cancer using human CAPRIN-1 protein

[0094] With the use of the human CAPRIN-1 protein (SEQ ID NO: 2) prepared in Example 2, the IgG antibody titer of the canine serum reacting with the human CAPRIN-1 protein was measured in the same manner as described above. When serum samples obtained from healthy dogs were subjected to the same measurement, the absorbance at 450 nm was not substantially observed as described above. The serum samples obtained from pancreatic cancer patient dogs of (1) exhibited a higher titer of the antibody against the human CAPRIN-1 protein than that of the control.

(3) Diagnosis of human pancreatic cancer

[0095] With the use of the human CAPRIN-1 protein (SEQ ID NO: 2) prepared in Example 2 and the anti-human IgG antibody, the IgG antibody titer of the serum samples obtained from healthy individuals reacting with the polypeptide was measured. The human CAPRIN-1 protein was immobilized by adding a recombinant protein solution diluted to 100 μg/ml with phosphate buffered saline to a 96-well immobilizer amino plate (Nunc) at 100 μl/well and then allowing the plate to stand at 4°C overnight. Blocking was performed in the following manner. That is, 4 g of Block Ace powder (DS PHARMA BIOMEDICAL Co., Ltd.) was dissolved in 100 ml of purified water, the solution was diluted 4-fold with purified water (hereafter, referred to as a "blocking solution"), the blocking solution was added at 100 μl/well, and the mixture was subjected to shaking at room temperature for 1 hour. Serum diluted 1000-fold with the blocking solution was added at 100 μl/well and then subjected to a reaction via shaking at room temperature for 3 hours. After washing the resultant 3 times with phosphate buffered saline containing 0.05% Tween 20 (Wako Pure Chemical Industries, Ltd.; this solution is referred to as "PBS-T" herein), an HRP-modified anti-human IgG antibody (HRP-Goat Anti-Human IgG (H+L) Conjugate: Zymed Laboratories) diluted 10000-fold with the blocking solution was added at 100 μl/well and then subjected to a reaction via shaking at room temperature for 1 hour. After the reaction product was washed 3 times with PBS-T, HRP substrate TMB (1-Step Turbo TMB (tetramethylbenzidine), PIERCE) was added at 100 μl/well, and an enzyme-substrate reaction was then performed at room temperature for 30 minutes. Thereafter, a 0.5 M sulfuric acid solution (Sigma Aldrich Japan) was added at 100 μl/well to terminate the reaction, and the absorbance at 450 nm was then measured using a microplate reader. An ovalbumin antigen adjusted to 50 μg/ml with phosphate buffered saline was immobilized and then used as a positive control. As a result, the absorbance at 450 nm was found to be high in the case of the ovalbumin antigen, although no absorbance (0) was detected in the case of the human CAPRIN-1 protein.

[0096] Further, the serum samples obtained from patients with pancreatic ductal carcinoma were subjected to measurement of the titer of the serum IgG antibody specifically reacting with the human CAPRIN-1 protein (the amino acid sequence of SEQ ID NO: 2) in the same manner as described above. As a result, the absorbance at 450 nm was found to be lower than the lowest detection limit in the case of healthy subjects, although it was found to be high in the case of patients with pancreatic cancer. With the use of the canine CAPRIN-1 protein (SEQ ID NO: 8) prepared in Example 2 and the anti-human IgG antibody, the titer of the human serum IgG antibody specifically reacting with the canine CAPRIN-1 protein was measured in the same manner as described above. As a result, pancreatic cancer patients were found to exhibit higher titers than healthy individuals.

[0097] Thus, it was demonstrated that human pancreatic cancer could be detected by the method of the present invention.

[Example 5] Diagnosis of pancreatic cancer using antibody against CAPRIN-1

(1) Diagnosis of pancreatic cancer by measuring CAPRIN-1 protein

[0098] With the use of the polyclonal antibody against the CAPRIN-1-derived peptide (SEQ ID NO: 43) obtained in Example 3 (1) in combination with each monoclonal antibody against the CAPRIN-1 protein obtained in Example 3 (2), Sandwich ELISA was carried out in order detect the CAPRIN-1 protein (cancer-bearing individual-derived serum) reacted positive upon cancer diagnosis using the CAPRIN-1 protein in Example 4 (1)-(3). The polyclonal antibody was used as a primary antibody and each monoclonal antibody was used as a secondary antibody. The amount of the proteins specifically reacting with each of the above antibodies in the sera was measured.

[0099] The primary antibody was immobilized by adding a polyclonal antibody solution diluted to 5 μg/ml with phosphate buffered saline to a 96-well immobilizer amino plate (Nunc) at 100 μl/well and shaking the plate at room temperature for 2 hours. Blocking was performed by adding a 50 mM sodium bicarbonate buffer solution (pH 8.4) (hereafter, referred to as a "blocking solution") containing 0.5% BSA (bovine serum albumin, Sigma Aldrich Japan) at 100 μl/well, followed by shaking at room temperature for 1 hour. Thereafter, the serum samples obtained from cancer-bearing individuals diluted with a blocking solution were added at 100 μl/well and then subjected to the reaction via shaking at room temperature for 3 hours. The dilution rate at this time was adjusted with 10-fold dilution series (i.e., 10-1000-fold dilutions). The reaction product was washed 3 times with phosphate buffered saline containing 0.05% Tween 20 (Wako Pure Chemical Industries, Ltd.; this solution is referred to as "PBS-T" herein), each monoclonal antibody as a secondary antibody diluted to a concentration of 1 μg/ml with the blocking solution was added at 100 μl/well, and the resultant was then subjected to shaking at room temperature for 1 hour for reaction. The reaction product was washed 3 times with PBS-T, an HRP-labeled anti-mouse IgG (H+L) antibody (Invitrogen) as a tertiary antibody diluted 5000-fold with the blocking solution was added at 100 μl/well, and the resultant was then allowed to stand at room temperature for 1 hour. After each well was washed 3 times with PBS-T, a TMB substrate solution (Thermo) was added at 100 μl per/well, and the resultant was allowed to stand for 15 to 30 minutes, so as to allow the color to develop. Thereafter, 1N sulfuric acid was added at 100 μl/well to terminate the reaction. The absorbance was measured at 450 nm using an spectrophotometer.

[0100] When the monoclonal antibodies #1 to #10 reacting with the surfaces of cancer cells were used as secondary antibodies, as a result, high absorbance values were detected in all the dogs with pancreatic ductal carcinoma, although no absorbance was detected in healthy dogs. When monoclonal antibodies that react with the CAPRIN-1 proteins but do not react with the surfaces of cancer cells were used as secondary antibodies, polypeptide values were detected in all specimens. However, all the absorbance values were lower than the detection limit, which were lower than the results for combinations of antibodies reacting with the surfaces of cancer cells.

[0101] Therefore, cancer can also be diagnosed or examined by this technique that comprises detection of the CAPRIN-1 proteins using antibodies against CAPRIN-1.

(2) Diagnosis or examination of cancer by measuring antigenic polypeptide on pancreatic cancer tissue by immunohistochemical staining

[0102] Immunohistochemical staining was performed using an array (BIOMAX) having 101 paraffin-embedded human pancreatic cancer tissue specimens. The array of human pancreatic cancer tissues was treated at 60°C for 3 hours, the resultant was put in a staining bottle filled with xylene, xylene was replaced with fresh xylene every 5 minutes, and this procedure was repeated 3 times. Subsequently, a similar procedure was carried out using ethanol and PBS-T instead of xylene. The array of human pancreatic cancer tissues was put in a staining bottle filled with 10 mM citrate buffer (pH 6.0) containing 0.05% Tween 20, treated at 125°C for 5 minutes, and then allowed to stand at room temperature for 40 minutes or longer. Excess water around each specimen was removed using Kimwipes, each section was encircled with DAKOPEN (DAKO), and an appropriate amount of Peroxidase Block (DAKO) was then added dropwise onto the array. The array was allowed to stand at room temperature for 5 minutes, the array was put in a staining bottle filled with PBS-T, and PBS-T was replaced with fresh PBS-T every 5 minutes. This procedure was performed 3 times. As a blocking solution, a PBS-T solution containing 10% FBS was applied onto the array, and the array was then allowed to stand in a moist chamber at room temperature for 1 hour. Subsequently, the monoclonal antibodies #1 to #10 prepared in Example 3 adjusted to 10 μg/ml with a PBS-T solution containing 5% FBS were applied onto the array, and the array was allowed to stand in a moist chamber at 4°C overnight. After the array was washed with PBS-T for 10 minutes 3 times, an appropriate amount of Peroxidase Labeled Polymer Conjugated (DAKO) was added dropwise onto the array, and the array was allowed to stand in a moist chamber at room temperature for 30 minutes. After the array was washed with PBS-T for 10 minutes 3 times, a DAB color-developing solution (DAKO) was applied onto the array, and the array was then allowed to stand at room temperature for about 10 minutes. After the color-developing solution was discarded, the array was washed with PBS-T for 10 minutes 3 times, rinsed with distilled water, successively put in 70%, 80%, 90%, 95%, and 100% ethanol solutions for 1 minute each, and then allowed to stand in xylene overnight. The glass slides were removed, coverslipped with Glycergel Mounting Medium (DAKO), and then observed. As a result, CAPRIN-1 expression was observed in pancreatic cancer cell membranes and in pancreatic cancer cells in the pancreatic cancer tissue samples with the use of any antibodies. When immunohistochemical staining was carried out with the use of Antibody #8, for example, strong CAPRIN-1 expression was observed in 54 specimens among the total pancreatic cancer tissue specimens (101 specimens) (i.e., 54%).

[0103] Similarly, immunohistochemical staining was carried out using an array (BIOMAX) of paraffin-embedded normal human tissues including normal human pancreatic tissues. Excess water around each specimen was removed using Kimwipes, each section was encircled with DAKOPEN (DAKO), and an appropriate amount of Peroxidase Block (DAKO) was then added dropwise onto the array. The array was allowed to stand at room temperature for 5 minutes, the array was put in a staining bottle filled with PBS-T, and PBS-T was replaced with fresh PBS-T every 5 minutes. This procedure was performed 3 times. As a blocking solution, a PBS-T solution containing 10% FBS was applied onto the array, and the array was then allowed to stand in a moist chamber at room temperature for 1 hour. Subsequently, the monoclonal antibodies #1 to #10 prepared in Example 3 adjusted to 10 μg/ml in a PBS-T solution containing 5% FBS were applied onto the array, and the array was then allowed to stand in a moist chamber at 4°C overnight. After the array was washed with PBS-T for 10 minutes 3 times, an appropriate amount of Peroxidase Labeled Polymer Conjugated (DAKO) was added dropwise onto the array, and the array was allowed to stand in a moist chamber at room temperature for 30 minutes. After the array was washed with PBS-T for 10 minutes 3 times, a DAB color-developing solution (DAKO) was applied onto the array, and the array was then allowed to stand at room temperature for about 10 minutes. After the color-developing solution was discarded, the array was washed with PBS-T for 10 minutes 3 times, rinsed with distilled water, successively put in 70%, 80%, 90%, 95%, and 100% ethanol solutions for 1 minute each, and then allowed to stand in xylene overnight. The glass slides were removed, coverslipped with Glycergel Mounting Medium (DAKO), and then observed. As a result, none of pancreas-derived normal tissue samples were stained and no CAPRIN-1 expression was observed, no matter what antibody was used.

Industrial Applicability

[0104] The present invention is industrially useful for diagnosis or detection of pancreatic cancer.

Free Text of Sequence Listing

[0105] SEQ ID NOs: 31 to 42: primers

SEQUENCE LISTING

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<120> Method for Detection of Pancreatic Cancer

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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

tcttcatacc tttttccatt ttgaatccta caaaaatact gcaaaagact agtgaatgtt 5529

taaaattaca ctagattaaa taatatgaaa gtc 5562

<210> 2

<211> 709
<212> PRT
<213> Homo sapiens

<400> 2

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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

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

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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<210> 3
<211> 3553
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (190)..(2274)
<223>

<400> 3

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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

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
```

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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

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

tagaacatat tctcttctca gaaaaagtgt ttttccaact gaaaattatt tttcaggtcc   2534

taaaacctgc taaatgtttt taggaagtac ttactgaaac atttttgtaa gacatttttg   2594

gaatgagatt gaacatttat ataaatttat tattcctctt tcatttttttt gaaacatgcc   2654

tattatattt tagggccaga caccctttaa tggccggata agccatagtt aacatttaga   2714
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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

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

cttgatgatg gtgcctggca catagtaggc actcaataaa tatttgttga atgaatgaa 3553

<210> 4
<211> 694
<212> PRT
<213> Homo sapiens

<400> 4

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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

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

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 Asn Ile Leu Trp Trp
690

<210> 5
<211> 1605
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (46)..(1392)
<223>

<400> 5

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gtcacaaata acttggagtt tgcaaaagaa ttacagagga gtttc atg gca tta agt      57
                                                    Met Ala Leu Ser
                                                    1

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
                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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<210> 6
<211> 448
<212> PRT
<213> Canis familiaris

<400> 6

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Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg
1               5                  10                  15

Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr
            20                  25                  30

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
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

<210> 7
<211> 4154
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(2154)
<223>

<400> 7

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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
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                    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
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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

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
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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 cacccttgct 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

ggagcactaa acgtttagat gcataccaaa ttatgcatgg gcccttaata taaaaggctg 2694

gctaccagct ttgacacagc actattcatc ctctggccaa acaactgtgg ttaaacaaca 2754

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gggctttgat tggcactttt tgaaaaatat gcaacaaata tgggatgtaa tctggatggc 2874

cgcttctgta cttaatgtga agtatttaga tacctttttg aacacttaac agtttcttct 2934

gacaatgact tttgtaagga ttggtactat ctatcattcc ttataatgta cattgtctgt 2994

cactaatcct cagatcttgc tgtattgtca cctaaattgg tacaggtact gatgaaaata 3054

tctaatggat aatcataaca ctcttggtca catgtttttc ctgcagcctg aaggtttta 3114

aaagaaaaag atatcaaatg cctgctgcta ccacccttt aaattgctat cttttgaaaa 3174

gcaccagtat gtgttttaga ttgatttccc tattttaggg aaatgacaga cagtagtttc 3234

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ccagtaggtg ctcagctact aaagaaaaac aaaaacaaga cacaaaacta ttctcaaaca 3774

ttcattgtta gacaactgga gtttttgctg gttttgtaac ctactaaaat ggataggctg 3834

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attggaaggg ttatctgttt acttttgcaa atgagtattt ctcttgctag cacctcccgt 4014

tgtgcgcttt aaatgacatc tgcctgggat gtaccacaac catatgttag ctgtatttta 4074

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tcctatatat aaaactaaat 4154

<210> 8
<211> 717
<212> PRT
<213> Canis familiaris

<400> 8

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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

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
            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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<210> 9
<211> 4939
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1) .. (2109)
<223>

<400> 9

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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
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        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
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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

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
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tcctagctcc taagtggagc ttctgttctg gccttggaag agctgttcca tagtctgcat   2169

gtaggttaca tgttaggaat acatttatca ttaccagact tgttgctagg gattaaatga   2229
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aatgctctgt ttctaaaact tctcttgaac ccaaatttaa ttttttgaat gactttccct 2289

gttactatat aaattgtctt gaaaactaga acatttctcc tcctcagaaa aagtgttttt 2349

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<213> Canis familiaris

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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
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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
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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
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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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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
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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
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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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Tyr Gln Arg Gly Cys Arg Lys
675

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cataaagaca ggactacaat tgtcagcttt atattacctg gatatggaag gaaactattt 2250

ttattctgca tgttcttcct aagcgtcatc ttgagccttg cacatgatac tcagattcct 2310

caccttgct 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 taccttttg 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 ccacccttt 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

<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

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
660 665 670

Tyr Gln Arg Gly Cys Arg Lys
675

<210> 13
<211> 2281
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(2154)
<223>

<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
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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
        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
```

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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
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<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

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

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
            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
```

<210> 15
<211> 3386
<212> DNA
<213> Bos taurus

<220>
<221> CDS
<222> (82)..(2208)
<223>

<400> 15

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cgcgtctcgc cccgtccacc gattgactcg ccgctcttgt ccttcctccc gctctttctt     60

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
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
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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

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
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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

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 ccacccttttt aaattgctat cttttgaaaa gcaccagtat   3248

gtgttttaga ttgatttccc tattttaggg aaatgacagt cagtagtttc acttctgatg   3308

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aaaaaaaaaa aaaaaaaa                                                 3386
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<213> Bos taurus

<400> 16

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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 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

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
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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

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
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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

Gln Gln Val Asn
705

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<211> 3150
<212> DNA
<213> Equus caballus

<220>

<221> CDS
<222> (1)..(1917)
<223>

<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
    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
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                    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
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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

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

ttttcatccc ataaagacag gactacagtt gtcagcttta tattacctgg atatggaagg   2097

aaactatttt tactctgcat gttctgtcct aagcgtcatc ttgagccttg cacatgatac   2157

tcagattcct ttcccttgct taggagtaaa acataatata ctttatgggg tgataatatc   2217

tccatagtta tttgaagtgg cttggaaaaa gcaagattga cttttgacat tggataaaat   2277

ctacaaatca gccctagagt ttcatggtca ttcacaaaac taaaatattt cccttgaaag   2337

gaagatggaa ggactggagt gtggtttggc agaacaactg catttcacag cttttcctat   2397

taaattggag cactgaatgt taaatgcata ccaaattatg catgggccct taatcacaca   2457

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aaacacgtgt aaattgcttt ttaacagctg atactgtaaa agacaaagct aaaatgcaaa   2577

attaggcttt cattggcact tttcgaaaaa tatgcaacaa atttgggatg taatctggat   2637

ggccacttct gtacttaatg tgaagtattt agataccttt ttgaacactt aacagtttct   2697

tcgacaatga cttttgtaag gattggtagt atatatcatt ccttatgaca tacattgtct   2757

gttgctaatc cttggatctt gctgtattgt cacctaaatt ggtacaggta ctgatgaaaa   2817

tctctcatgg ataaacctaa cactcttcgt cacatgtttt tcctgcagcc tgaaggtttt   2877
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aagcaccagt atgtgttttt agattgattt ccctatttta gggaaatgac agtcagtagt 2997

ttcagttctg atggtataag caaagcaaat aaaacgtgtt tataaaagtt gtatcttgaa 3057

acactggtgt tcaacagcta gcagcttctg tggttcaccc cctgccttgt tagtgttacc 3117

catttatggt tatctccagc agcaatttct cta 3150

<210> 18
<211> 638
<212> PRT
<213> Equus caballus

<400> 18

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Met Glu Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu
1               5                  10                  15

Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val
            20                  25                  30

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
                85                  90                  95

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
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```
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
    210                 215                 220

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
        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
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```
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
            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
    610                 615                 620

Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
625                 630                 635
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cggggacagg gcgaagcggc ctgcgcccac ggagcgcacg tctctgttct caacgcagca 120

ccacccttgc ccccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg 178

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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
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
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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
    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
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        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
                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 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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gcaaaactgc atttcatagc tttcccatta aattggagca ccgacagatt aaaagcatac   2822
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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
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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

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
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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
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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

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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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
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```
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
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    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

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
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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

ttaatcgcca aaaacacact ggccagtgta ccataatatg ttaccagaag agttattatc   2342

tatttgttct ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca   2402

ggactgcaat tgtcagcttt acattacctg gatatggaag gaaactattt ttattctgca   2462

tgttctgtcc taagcgtcat cttgagcctt gcacacaata caatactcag attcctcacc   2522

cttgcttagg agtaaaacat tatatactta tggggtgata atatctccat agttagttga   2582

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aaggagtgga gtgtggttta gcaaaactgc atttcatagc tttcccatta aattggagca   2762

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ttgattggct cttctggaaa atatgcatca aatatggggg ataatctgga tgggctgctg   3002
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gacaactgga gtttttgctg gttttgtagc ctactaaaac tgctgaggct gttgaacatt 3962

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cggtatgatc tggaaagact tgattgaaag ataattcagc tgacataagg atgagtgagg 5882

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ttgtctcaac atttggaagc tattgaaggt tttaaaatgg tgtgtattgt tttttttgg 6062

ggggggggtg gccagaatag tgggtcatct aataaaactg ccatttaaaa gatcaaaaaa 6122

aaaaaaaaaa aaaaaaaaa 6141

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<211> 707
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<213> Mus musculus

<400> 22

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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
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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
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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

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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

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

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
            495                 500                 505

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
    525                 530                 535

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
540                 545                 550                 555

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
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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
620                 625                 630                 635

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
                640                 645                 650

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
            655                 660                 665

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

tgtgatacac aggattatgt ttaatcgcca aaaacacact ggccagtgta ccataatatg   2295

ttaccagaag agttattatc tatttgttct ccctttcagg aaacttattg taaagggact   2355

gttttcatcc cataaagaca ggactgcaat tgtcagcttt acattacctg gatatggaag   2415

gaaactattt ttattctgca tgttctgtcc taagcgtcat cttgagcctt gcacacaata   2475

caatactcag attcctcacc cttgcttagg agtaaaacat tatatactta tggggtgata   2535

atatctccat agttagttga agtggcttgg aaaaaaaatg caagattgaa tttttgacct   2595

tggataaaat ctacaatcag ccctagaact attcagtggt aattgacaaa gttaaagcat   2655

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actcacacaa gtgaggctgg ctaccagcct tgacatagca ctcactagtc ttctggccaa   2835

acgactgtga ttaaaacaca tgtaaattgc tctttagtag tggatactgt gtaagacaaa   2895

gccaaattgc aaatcaggct ttgattggct cttctggaaa atatgcatca aatatggggg   2955

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taacagtttc tctgaacaat gacttacatg gggattggtc ctgtttgtca ttcctcacca   3075

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ggtactgatg gaaatcgcta atggatggat aatcataaca cttttggtca catgttttct   3195

cctgcagcct gaaagttctt aaagaaaaag atatcaaatg cctgctgcta ccacccttt    3255

aaattgctat ctttagaaaa gcaccggtat gtgttttaga ttcatttccc tgttttaggg   3315
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gctagtgtca cagcctttgg ttatgtctag tagctgtttc tgaagtattt tcatttatct 3495

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tgtgtattgt tttttttgg gggggggtg gccagaatag tgggtcatct aataaaactg 6075

ccatttaaaa gatcaaaaaa aaaaaaaaaa aaaaaaaaa 6114

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<213> Mus musculus

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            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
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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

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
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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

Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro
        435                 440                 445

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
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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
660 665 670

Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly
675 680 685

Met Pro Gln Met Asn Thr Gln Gln Val Asn
690 695

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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
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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
        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
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    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
    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
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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

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ggaagtacct actgaaactt tttgtaagac atttttggaa cgagcttgaa catttatata   2597

aatttattac cctctttgat ttttgaaaca tgcatattat atttaggctg agaagccctt   2657

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ctaaacttga acacttttag gaccaatgtt agtgttctaa ataccaacat atttctgatg   2777

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gttattttaa ctgttacaag tcattataca attttgaatg ttctgtagtt tcttttaac    3317

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gtcacttcct attgaaatgt aagctagcgt gtaccttaga atgtgagctc catgagagca   3437

ggtaccttgt ttgtcttcac tgctgtatct attcccaacg cctcatgaca gtgcctggca   3497

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<211> 692
<212> PRT

<213> Mus musculus

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            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
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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
```

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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

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<221> CDS
<222> (139)..(2217)
<223>

<400> 27

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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
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                                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
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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

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
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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
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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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<212> PRT
<213> Mus musculus

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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
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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 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
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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

<210> 29
<211> 2109
<212> DNA
<213> Gallus gallus

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

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                    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
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```
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
```

<210> 30
<211> 702
<212> PRT
<213> Gallus gallus

<400> 30

```
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

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

<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> 27
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 37
catatggcat taagtcaaga tattcag 27

<210> 38
<211> 23
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 38
ggtacctttg cggcatccct ctg 23

<210> 39
<211> 21
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 39
catatgccgt cggccaccag c 21

<210> 40
<211> 22
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 40
ggtaccattc acttgctgag tg 22

<210> 41
<211> 23
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 41
gagctcatgc cctcggccac cag 23

<210> 42

<211> 23
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 42
ctcgagttaa ttcacttgct gag 23

<210> 43
<211> 14
<212> PRT
<213> Homo sapiens

<400> 43

Arg Asn Leu Glu 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
```

<210> 56
<211> 94
<212> PRT
<213> Mus musculus

<400> 56

```
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> 57
<211> 111
<212> PRT
<213> Mus musculus

<400> 57

```
Pro Ala Cys Leu Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser
1               5                  10                  15

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
              100                 105                 110
```

<210> 58
<211> 102
<212> PRT
<213> Mus musculus

<400> 58

```
Arg Leu Pro Phe Tyr Ser Leu Glu Gln Arg Ala Thr Ile Ser Tyr Arg
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> 101
<212> PRT
<213> Mus musculus

<400> 59

```
Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Met His
1               5                  10                  15

Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Met Ile
            20                  25                  30

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

Ala Thr Leu Asn Val Asp Lys Ser Ser Asn Thr Ala Tyr Met Gln Leu
    50                  55                  60

Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Gly
65                  70                  75                  80

Leu Arg His Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
                85                  90                  95

Thr Val Ser Ser Lys
            100
```

<210> 60
<211> 99
<212> PRT
<213> Mus musculus

<400> 60

```
Thr Ile Leu Trp Arg Glu Gly Pro Phe Ser Tyr Arg Ala Ser Lys Ser
1               5                  10                  15

Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro
            20                  25                  30

Gly Gln Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser
        35                  40                  45

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    50                  55                  60

Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys
65                  70                  75                  80

Gln His Ile Arg Glu Leu Thr Arg Ser Glu Glu Val Pro Ser Trp Arg
                85                  90                  95

Ser Asn Lys
```

<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> 11
<212> PRT
<213> Homo sapiens

<400> 63

```
Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg
1               5                   10
```

Claims

1. A method for detecting pancreatic cancer, comprising measuring, in a sample separated from a subject:

   (i) the presence or an amount of a polypeptide having a reactivity of specifically binding to an antibody against a CAPRIN-1 protein via an antigen-antibody reaction, or
   (ii) an antibody against CAPRIN-1 protein, or
   (iii) the presence or an amount of a nucleic acid encoding CAPRIN-1 protein,

   wherein said CAPRIN-1 protein consists of an amino acid sequence represented by any of the even-numbered SEQ ID Nos: 2 to 30.

2. The method according to claim 1, wherein the polypeptide is a CAPRIN-1 protein consisting of an amino acid sequence represented by any of the even-numbered SEQ ID NOs: 2 to 30, or a polypeptide consisting of an amino acid sequence having 85-90% or higher sequence identity with the CAPRIN-1 protein.

3. The method according to claim 1 or 2, wherein the subject is a human or a dog.

4. The method according to claim 3, wherein the subject is a dog and the CAPRIN-1 protein comprises the amino acid sequence represented by SEQ ID NO: 6, 8, 10, 12, or 14.

5. The method according to claim 3, wherein the subject is a human and the CAPRIN-1 protein comprises the amino acid sequence represented by SEQ ID NO: 2 or 4.

6. The method according to any one of claims 1 to 5, wherein the presence or amount of the nucleic acid in the sample is measured using a polynucleotide specifically hybridizing to a partial sequence comprising 15-19 or more nucleotides or 20-30 or more nucleotides in the nucleotide sequence of the nucleic acid or a sequence complementary thereto.

7. The method according to claim 6, wherein the subject is a dog and the polynucleotide specifically hybridizes to a partial sequence comprising 15-19 or more nucleotides or 20-30 or more nucleotides in the nucleotide sequence represented by SEQ ID NO: 5, 7, 9, 11, or 13 or a sequence complementary thereto.

8. The method according to claim 6, wherein the subject is a human and the polynucleotide specifically hybridizes to a partial sequence comprising 15-19 or more nucleotides or 20-30 or more nucleotides in the nucleotide sequence represented by SEQ ID NO: 1 or 3 or a sequence complementary thereto.

9. The method according to any one of claims 1 to 5, wherein the presence or amount of the polypeptide is determined by measuring the polypeptide contained in the sample in an immunological assay.

10. The method according to any one of claims 1 to 9, wherein the sample is blood, serum, blood plasma, ascites fluid, pleural effusion, tissues, or cells.

11. The method according to any one of claims 1 to 10, wherein the antibody that undergoes an antigen-antibody reaction with the polypeptide is an antibody that binds to the surface of a pancreatic cancer cell.

12. The method according to any one of claims 1 to 11, wherein the antibody that undergoes an antigen-antibody reaction with the polypeptide comprises an antibody having an immunological reactivity with a polypeptide consisting of an amino acid sequence comprising at least 7 to 12 continuous amino acid residues within the region of amino acid residue Nos. 50 to 98 or amino acid residue Nos. 233 to 344 of the amino acid sequence represented by any of even-numbered SEQ IDS NO: 2 to 30 except for SEQ ID NOs: 6 and 18.

13. The method according to any one of claims 1 to 12, wherein the antibody that undergoes an antigen-antibody reaction with the polypeptide is one or more antibodies selected from the group consisting of: an antibody binding to a polypeptide comprising the amino acid sequence represented by SEQ ID NO: 43; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 44 and 45; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 44 and 46; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 44 and 47; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 44 and 48; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 49 and 50; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 51 and 52; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 53 and 54; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 55 and 56; a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 57 and 58; and a monoclonal antibody comprising the amino acid sequences represented by SEQ ID NOs: 59 and 60.

14. The method according to any one of claims 1 to 10, which uses a reagent or kit comprising one or more polynucleotides that specifically hybridize to a partial sequence comprising 15 to 19 or more nucleotides or 20 to 30 or more nucleotides in the nucleotide sequence represented by any of the odd-numbered SEQ ID NOs: 1 to 29 and encoding a CAPRIN-1 protein or in a sequence complementary to the nucleotide sequence.

Patentansprüche

1. Verfahren zur Detektion von Pankreaskrebs, das in einer von einem Individuum gewonnenen Probe das Messen

   (i) des Vorliegens oder einer Menge eines Polypeptids, das eine Reaktivität in Bezug auf die spezifische Bindung an einen Antikörper gegen ein CAPRIN-1-Protein über eine Antigen-Antikörper-Reaktion aufweist, oder
   (ii) eines Antikörpers gegen CAPRIN-1-Protein oder
   (iii) des Vorliegens oder einer Menge einer für CAPRIN-1-Protein kodierenden Nucleinsäure

   umfasst, worin das CAPRIN-1-Protein aus einer beliebigen der geradzahligen Seq.-ID Nr. 2 bis 30 Aminosäuresequenzen besteht.

2. Verfahren nach Anspruch 1, worin das Polypeptid ein CAPRIN-1-Protein ist, das aus einer durch eine beliebige der geradzahligen Seq.-ID Nr. 2 bis 30 dargestellten Aminosäuresequenz besteht, oder ein Polypeptid ist, das aus einer Aminosäuresequenz mit 85-90 % oder höherer Sequenzidentität mit CAPRIN-1-Protein besteht.

3. Verfahren nach Anspruch 1 oder 2, worin das Individuum ein Mensch oder ein Hund ist.

4. Verfahren nach Anspruch 3, worin das Individuum ein Hund ist und das CAPRIN-1-Protein die Aminosäuresequenz der Seq.-ID Nr. 6, 8, 10, 12 oder 14 umfasst.

5. Verfahren nach Anspruch 3, worin das Individuum ein Mensch ist und das CAPRIN-1-Protein die Aminosäuresequenz der Seq.-ID Nr. 2 oder 4 umfasst.

6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Vorliegen oder die Menge der Nucleinsäure in der Probe unter Verwendung eines Polynucleotids gemessen wird, das spezifisch an eine Teilsequenz, die 15 bis 19 oder mehr Nucleotide oder 20 bis 30 oder mehr Nucleotide umfasst, in der Nucleotidsequenz der Nucleinsäure oder

einer zu dieser komplementären Sequenz hybridisiert.

7. Verfahren nach Anspruch 6, worin das Individuum ein Hund ist und das Polynucleotid an eine Teilsequenz, die 15 bis 19 oder mehr Nucleotide oder 20 bis 30 oder mehr Nucleotide umfasst, in der Nucleotidsequenz mit Seq.-ID Nr. 5, 7, 9, 11 oder 13 oder einer zu dieser komplementären Sequenz spezifisch hybridisiert.

8. Verfahren nach Anspruch 6, worin das Individuum ein Hund ist und das Polynucleotid an eine Teilsequenz, die 15 bis 19 oder mehr Nucleotide oder 20 bis 30 oder mehr Nucleotide umfasst, in der Nucleotidsequenz mit Seq.-ID Nr. 1 oder 3 oder einer zu dieser komplementären Sequenz spezifisch hybridisiert.

9. Verfahren nach einem der Ansprüche 1 bis 5, worin das Vorliegen oder die Menge des Polypeptids durch das Messen des in der Probe enthaltenen Polypeptids in einem immunologischen Test ermittelt wird.

10. Verfahren nach einem der Ansprüche 1 bis 9, worin es sich bei der Probe um Blut, Serum, Blutplasma, Aszitesflüssigkeit, Pleuraerguss, Gewebe oder Zellen handelt.

11. Verfahren nach einem der Ansprüche 1 bis 10, worin der Antikörper, der eine Antigen-Antikörper-Reaktion mit dem Polypeptid durchläuft, ein Antikörper ist, der an die Oberfläche einer Pankreaskrebszelle bindet.

12. Verfahren nach einem der Ansprüche 1 bis 11, worin der Antikörper, der eine Antigen-Antikörper-Reaktion mit dem Polypeptid durchläuft, einen Antikörper mit einer immunologischen Reaktivität mit einem Polypeptid umfasst, das aus einer Aminosäuresequenz besteht, die zumindest 7 bis 12 zusammenhängende Aminosäurereste innerhalb der Region der Aminosäurereste Nr. 50 bis 98 oder der Aminosäurereste Nr. 233 bis 344 der Aminosäuresequenz einer beliebigen der geradzahligen Seq.-ID Nr. 2 bis 30 mit Ausnahme von Seq.-ID Nr. 6 und 18 umfasst.

13. Verfahren nach einem der Ansprüche 1 bis 12, worin der Antikörper, der eine Antigen-Antikörper-Reaktion mit dem Polypeptid durchläuft, ein oder mehrere Antikörper ausgewählt aus der aus folgenden bestehenden Gruppe ist: einem Antikörper, der an ein Polypeptid bindet, das die Aminosäuresequenz der Seq.-ID Nr. 43 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 44 und 45 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 44 und 46 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 44 und 47 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 44 und 48 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 49 und 50 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 51 und 52 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 53 und 54 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 55 und 56 umfasst; einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 57 und 58 umfasst; und einem monoklonalen Antikörper, der die Aminosäuresequenzen der Seq.-ID Nr. 59 und 60 umfasst.

14. Verfahren nach einem der Ansprüche 1 bis 10, bei dem ein Reagens oder ein Set verwendet wird, das ein oder mehrere Polynucleotide umfasst, die an eine Teilsequenz, die 15 bis 19 oder mehr Nucleotide oder 20 bis 30 oder mehr Nucleotide umfasst, in der Nucleotidsequenz einer der ungeradzahligen Seq.-ID Nr. 1 bis 29 spezifisch bindet und für ein CAPRIN-1-Protein kodiert oder in einer zu der Nucleotidsequenz komplementären Sequenz.

Revendications

1. Procédé de détection du cancer du pancréas, comprenant la mesure, dans un échantillon isolé chez un sujet, de :

   (i) la présence ou une quantité d'un polypeptide possédant une réactivité de liaison spécifique à un anticorps dirigé contre une protéine CAPRINE-1 via une réaction antigène-anticorps, ou
   (ii) un anticorps dirigé contre une protéine CAPRINE-1, ou
   (iii) la présence ou une quantité d'un acide nucléique codant pour une protéine CAPRINE-1,

   où ladite protéine CAPRINE-1 consiste en une séquence d'acides aminés représentée par l'une quelconque des SEQ ID NO: 2 à 30 de numéro pair.

2. Procédé selon la revendication 1, dans lequel le polypeptide est une protéine CAPRINE-1 consistant en une séquence d'acides aminés représentée par l'une quelconque des SEQ ID NO: 2 à 30 de numéro pair, ou un polypeptide

consistant en une séquence d'acides aminés présentant 85-90 % d'identité de séquence ou plus avec la protéine CAPRINE-1.

3. Procédé selon la revendication 1 ou 2, dans lequel le sujet est un humain ou un chien.

4. Procédé selon la revendication 3, dans lequel le sujet est un chien et la protéine CAPRINE-1 comprend la séquence d'acides aminés représentée par SEQ ID NO: 6, 8, 10, 12, ou 14.

5. Procédé selon la revendication 3, dans lequel le sujet est un humain et la protéine CAPRINE-1 comprend la séquence d'acides aminés représentée par SEQ ID NO: 2 ou 4.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel la présence ou la quantité de l'acide nucléique dans l'échantillon est mesurée en utilisant un polynucléotide qui s'hybride spécifiquement à une séquence partielle comprenant 15-19 nucléotides ou plus ou 20-30 nucléotides ou plus dans la séquence de nucléotides de l'acide nucléique ou une séquence complémentaire à celle-ci.

7. Procédé selon la revendication 6, dans lequel le sujet est un chien et le polynucléotide s'hybride spécifiquement à une séquence partielle comprenant 15-19 nucléotides ou plus ou 20-30 nucléotides ou plus dans la séquence de nucléotides représentée par SEQ ID NO: 5, 7, 9, 11, ou 13 ou une séquence complémentaire à celles-ci.

8. Procédé selon la revendication 6, dans lequel le sujet est un humain et le polynucléotide s'hybride spécifiquement à une séquence partielle comprenant 15-19 nucléotides ou plus ou 20-30 nucléotides ou plus dans la séquence de nucléotides représentée par SEQ ID NO: 1 ou 3 ou une séquence complémentaire à celles-ci.

9. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel la présence ou la quantité du polypeptide est déterminée en mesurant le polypeptide contenu dans l'échantillon dans un dosage immunologique.

10. Procédé selon l'une quelconque des revendications 1 à 9, dans lequel l'échantillon est du sang, du sérum, du plasma sanguin, du liquide d'ascite, un épanchement pleural, des tissus, ou des cellules.

11. Procédé selon l'une quelconque des revendications 1 à 10, dans lequel l'anticorps qui subit une réaction antigène-anticorps avec le polypeptide est un anticorps qui se lie à la surface d'une cellule du cancer du pancréas.

12. Procédé selon l'une quelconque des revendications 1 à 11, dans lequel l'anticorps qui subit une réaction antigène-anticorps avec le polypeptide comprend un anticorps possédant une réactivité immunologique avec un polypeptide consistant en une séquence d'acides aminés comprenant au moins 7 à 12 résidus d'acides aminés continus au sein de la région des résidus d'acides aminés n° 50 à 98 ou des résidus d'acides aminés n° 233 à 344 de la séquence d'acides aminés représentée par l'une quelconque des SEQ ID NO: 2 à 30 de numéro pair à l'exception des SEQ ID NO: 6 et 18.

13. Procédé selon l'une quelconque des revendications 1 à 12, dans lequel l'anticorps qui subit une réaction antigène-anticorps avec le polypeptide est un ou plusieurs anticorps sélectionnés dans le groupe consistant en : un anticorps qui se lie à un polypeptide comprenant la séquence d'acides aminés représentée par SEQ ID NO: 43 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 44 et 45 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 44 et 46 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 44 et 47 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 44 et 48 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 49 et 50 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 51 et 52 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 53 et 54 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 55 et 56 ; un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 57 et 58 ; et un anticorps monoclonal comprenant les séquences d'acides aminés représentées par SEQ ID NO: 59 et 60.

14. Procédé selon l'une quelconque des revendications 1 à 10, qui utilise un réactif ou un kit comprenant un ou plusieurs polynucléotides qui s'hybrident spécifiquement à une séquence partielle comprenant 15 à 19 nucléotides ou plus ou 20 à 30 nucléotides ou plus dans la séquence de nucléotides représentée par l'une quelconque des SEQ ID NO: 1 à 29 de numéro impair et codant pour une protéine CAPRINE-1 ou dans une séquence complémentaire à

la séquence de nucléotides.

REFERENCES CITED IN THE DESCRIPTION

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ELJÁRÁS HASNYÁLMIRIGYRÁK DETEKTÁLÁSÁRA

Szabadalmi igénypontok

1. Eljárás hasnyálmirigyrák detektálására, amely eljárás során egy alanytól levett mintában mérjük:

   (i) egy CAPRIN-1 fehérje elleni antitesthez való, antigén-antitest reakción keresztüli specifikus kötődésre vonatkozó reaktivitással rendelkező polipeptid jelenlétét vagy mennyiségét, vagy
   (ii) CAPRIN-1 fehérje elleni antitestet, vagy
   (iii) CAPRIN-1 fehérjét kódoló nukleinsav jelenlététét vagy mennyiségét,

   ahol a CAPRIN-1 fehérje a SEQ ID NO: 2 - 30 (azaz a 2 - 30 azonosítási számú szekvenciák) közül a páros azonosítási számúak bármelyike által bemutatott aminosav-szekvenciából áll.

2. Az 1. igénypont szerinti eljárás, ahol a polipeptid olyan CAPRIN-1 fehérje, amely a SEQ ID NO: 2 - 30 közül a páros azonosítási számúak bármelyike által bemutatott aminosav-szekvenciából áll, vagy olyan polipeptid, amely a CAPRIN-1 fehérjével 85-90%-os vagy afeletti szekvenciaazonosságot mutató aminosav-szekvenciából áll.

3. Az 1. vagy 2. igénypont szerinti eljárás, ahol az alany ember vagy kutya.

4. A 3. igénypont szerinti eljárás, ahol az alany kutya, és a CAPRIN-1 fehérje tartalmazza a SEQ ID NO: 6, 8, 10, 12 vagy 14 által bemutatott aminosav-szekvenciát.

5. A 3. igénypont szerinti eljárás, ahol az alany ember, és a CAPRIN-1 fehérje tartalmazza a SEQ ID NO: 2 vagy 4 által bemutatott aminosav-szekvenciát.

6. Az 1-5. igénypontok bármelyike szerinti eljárás, ahol a nukleinsav jelenlétét vagy mennyiségét a mintában a nukleinsav vagy azzal komplementer szekvencia nukleotidszekvenciájából 15-19 vagy több nukleotidot vagy 20-30 vagy több nukleotidot tartalmazó parciális szekvenciához specifikusan hibridizáló polinukleotid alkalmazásával mérjük.

7. Az 6. igénypont szerinti eljárás, ahol az alany kutya, és a polinukleotid specifikusan hibridizál egy a SEQ ID NO: 5, 7, 9, 11 vagy 13 által bemutatott vagy azzal komplementer nukleotidszekvenciából 15-19 vagy több nukleotidot vagy 20-30 vagy több nukleotidot tartalmazó parciális szekvenciához.

8. Az 6. igénypont szerinti eljárás, ahol az alany ember, és a polinukleotid specifikusan hibridizál egy a SEQ ID NO: 1 vagy 3 által bemutatott vagy azzal komplementer nukleotidszekvenciából 15-19 vagy több nukleotidot vagy 20-30 vagy több nukleotidot tartalmazó parciális szekvenciához.

9. Az 1-5. igénypontok bármelyike szerinti eljárás, ahol a polipeptid jelenlétét vagy mennyiségét úgy határozzuk meg, hogy immunológiai vizsgálattal mérjük a mintában lévő polipeptidet.

10. Az 1-9. igénypontok bármelyike szerinti eljárás, ahol a minta vér, szérum, vérplazma, aszciteszfolyadék, pleurális effúzió, szövetek vagy sejtek.

11. Az 1-10. igénypontok bármelyike szerinti eljárás, ahol a polipeptiddel antigén-antitest reakción átmenő antitest olyan antitest, amely képes kötődni egy hasnyálmirigyrák-sejt felszínéhez.

12. Az 1-11. igénypontok bármelyike szerinti eljárás, ahol a polipeptiddel antigén-antitest reakción átmenő antitest tartalmaz olyan antitestet, amely immunológiai reaktivitást mutat egy olyan polipeptiddel, amely olyan aminosav-szekvenciából áll, amely tartalmaz legalább 7-12 szomszédos aminosavmaradékot a SEQ ID NO: 2 - 30 közül a SEQ ID NO: 6 és 18 kivételével a páros azonosítási számúak bármelyike által bemutatott

aminosav-szekvencia 50-98. aminosavmaradékai által alkotott régióból vagy 233-344. aminosavmaradékai által alkotott régióból.

13. Az 1-12. igénypontok bármelyike szerinti eljárás, ahol a polipeptiddel antigén-antitest reakción átmenő antitest egy vagy több antitest, amelyet a következők által alkotott csoportból választunk: antitest, amely képes kötődni egy polipeptidhez, amely tartalmazza a SEQ ID NO: 43 által bemutatott aminosav-szekvenciát; monoklonális antitest, amely tartalmazza a SEQ ID NO: 44 és 45 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 44 és 46 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 44 és 47 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 44 és 48 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 49 és 50 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 51 és 52 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 53 és 54 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 55 és 56 által bemutatott aminosav-szekvenciákat; monoklonális antitest, amely tartalmazza a SEQ ID NO: 57 és 58 által bemutatott aminosav-szekvenciákat; és monoklonális antitest, amely tartalmazza a SEQ ID NO: 59 és 60 által bemutatott aminosav-szekvenciákat.

14. Az 1-10. igénypontok bármelyike szerinti eljárás, amely használ olyan reagenst vagy készletet (kitet), amely tartalmaz egy vagy több olyan polinukleotidot, amely specifikusan hibridizál egy a SEQ ID NO: 1 - 29 közül a páratlan azonosítási számúak bármelyike által bemutatott és egy CAPRIN-1 fehérjét kódoló nukleotidszekvenciából vagy a nukleotidszekvenciával komplementer szekvenciából 15-19 vagy több nukleotidot vagy 20-30 vagy több nukleotidot tartalmazó parciális szekvenciához.