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(54) **COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF BREAST CANCER**

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(57) **ABSTRACT**

The invention relates to nucleic acid molecules and proteins associated with breast cancer. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human breast cancers are provided.

## COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF BREAST CANCER

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 10/855,588, filed on May 26, 2004, the entire contents of which are expressly incorporated herein by reference. This application also claims the benefit of U.S. Provisional Application No. 60/474,281, filed May 29, 2003, and U.S. Provisional Application No. 60/555,557, filed Mar. 23, 2004, the entire contents of each of which are expressly incorporated herein by reference.

### FIELD OF THE INVENTION

[0002] The field of the invention is breast cancer, including diagnosis, characterization, management, and therapy of breast cancer.

### BACKGROUND OF THE INVENTION

[0003] The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

[0004] The incidence of breast cancer, a leading cause of death in women, has been gradually increasing in the United States over the last thirty years. In 1997, it was estimated that 181,000 new cases were reported in the U.S., and that 44,000 people would die of breast cancer (Parker et al., 1997, *CA Cancer J. Clin.* 47:5-27; Chu et al., 1996, *J. Nat. Cancer Inst.* 88:1571-1579). While the pathogenesis of breast cancer is unclear, transformation of normal breast epithelium to a malignant phenotype may be the result of genetic factors, especially in women under 30 (Mild et al., 1994, *Science*, 266:66-71). The discovery and characterization of BRCA1 and BRCA2 has recently expanded our knowledge of genetic factors which can contribute to familial breast cancer. Germ-line mutations within these two loci are associated with a 50 to 85% lifetime risk of breast and/or ovarian cancer (Casey, 1997, *Curr. Opin. Oncol.* 9:88-93; Marcus et al., 1996, *Cancer* 77:697-709). However, it is likely that other, non-genetic factors also have a significant effect on the etiology of the disease. Regardless of its origin, breast cancer morbidity and mortality increases significantly if it is not detected early in its progression. Thus, considerable effort has focused on the early detection of cellular transformation and tumor formation in breast tissue.

[0005] Currently, the principal manner of identifying breast cancer is through detection of the presence of dense tumorous tissue. This may be accomplished to varying degrees of effectiveness by direct examination of the outside of the breast, or through mammography or other X-ray imaging methods (Jatoi, 1999, *Am. J. Surg.* 177:518-524). The latter approach is not without considerable cost, however. Every time a mammogram is taken, the patient incurs a small risk of having a breast tumor induced by the ionizing properties of the radiation used during the test. In addition, the process is expensive

and the subjective interpretations of a technician can lead to imprecision, e.g., one study showed major clinical disagreements for about one-third of a set of mammograms that were interpreted individually by a surveyed group of radiologists. Moreover, many women find that undergoing a mammogram is a painful experience. Accordingly, the National Cancer Institute has not recommended mammograms for women under fifty years of age, since this group is not as likely to develop breast cancers as are older women. It is compelling to note, however, that while only about 22% of breast cancers occur in women under fifty, data suggests that breast cancer is more aggressive in pre-menopausal women.

[0006] It would therefore be beneficial to provide specific methods and reagents for the diagnosis, staging, prognosis, monitoring, and treatment of diseases associated with breast cancer, or to indicate a predisposition to such for preventative measures.

### SUMMARY OF THE INVENTION

[0007] The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Table 1 and Table 2. The invention provides nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such marker proteins and/or fragments of the marker proteins.

[0008] The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating breast cancer. In one embodiment, the invention provides a diagnostic method of assessing whether a patient has breast cancer or has higher than normal risk for developing breast cancer, comprising comparing the level of expression of at least one marker of the invention in a patient sample and the normal level of expression of the marker or markers in a control, e.g., a sample from a patient without breast cancer. Elevated expression of the marker or markers in the patient sample can be indicative of a patient having or at risk for developing breast cancer.

[0009] In another embodiment, the invention provides a diagnostic method of assessing whether a patient has an aggressive breast tumor or is likely to develop an aggressive breast tumor, comprising comparing the level of expression of at least one marker of the invention in a patient sample and the level of expression of the marker in a sample from a control subject having an indolent breast tumor or no breast tumor. Elevated expression of the marker can be indicative of aggressive breast cancer.

[0010] Thus, the methods of the present invention can be of use in identifying patients having an enhanced risk of developing breast cancer (e.g., patients having a familial history of breast cancer, patients identified as having a mutant oncogene). The methods are also useful diagnostics for assessing whether a patient has an aggressive breast cancer or is likely to develop an aggressive breast tumor.

[0011] The methods of the present invention may be useful in predicting the specific stage of breast cancer, as well as in assessing whether the cancer has metastasized (e.g., metastasis to the lymph nodes). Still further, the methods of the present invention are also useful in predicting the clinical outcome for a patient with breast cancer, or for a patient who has undergone therapy to eradicate breast cancer. Additionally, the methods of the present invention are also useful in

assessing the efficacy of treatment of a breast cancer patient (e.g., the efficacy of chemotherapy).

**[0012]** According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred are embodiments of the method wherein the marker is over-expressed by at least five-fold in at least about 15% of breast cancer patients (including, e.g., stage 0 breast cancer patients, stage I breast cancer patients, stage IIA breast cancer patients, stage IIB breast cancer patients, stage IIIA breast cancer patients, stage IIIB breast cancer patients, stage IV breast cancer patients, grade I breast cancer patients, grade II breast cancer patients, grade III breast cancer patients, malignant breast cancer patients, ductal carcinoma breast cancer patients, and lobular carcinoma breast cancer patients, and any other types of cancers, malignancies and transformations associated with the breast) as compared to normal non-breast cancer patients.

**[0013]** In one aspect, a diagnostic method of assessing whether a patient is afflicted with breast cancer (e.g., new detection "screening," detection of recurrence, reflex testing) is provided. Such method comprises comparing the level of expression of at least one marker listed in Table 1 in a sample from the patient, and the level of expression of the marker or markers in a control subject not having breast cancer. A significantly higher level of expression of the marker in the patient sample, as compared to the level in the control subject, is an indication that the patient is afflicted with breast cancer.

**[0014]** The invention additionally provides a diagnostic method for assessing whether a patient is afflicted with an aggressive breast cancer, comprising the steps of:

**[0015]** determining the level of expression of at least one marker in a patient sample, wherein the marker is selected from the group consisting of the markers listed in Table 2;

**[0016]** determining the level of expression of the marker or markers in a sample from a control subject having an indolent breast tumor or no breast tumor; and

**[0017]** comparing the level of expression of the marker in the patient sample and in the sample from a control subject. A significantly higher level of expression of the marker or markers in the patient sample, as compared to the level in the sample from the control subject, is an indication that the patient has an aggressive breast cancer or is likely to develop an aggressive breast tumor. No difference in expression between the patient sample and the control sample, or a significantly lower level of expression in the patient sample, as compared to the control level, indicates that the patient has an indolent breast cancer.

**[0018]** The invention further provides a diagnostic method of assessing whether a patient is afflicted with a breast cancer which has metastasized or is likely to metastasize, the method comprising comparing the level of expression of at least one marker listed in Table 2 in a sample from the patient, and the level of expression of the marker or markers in a sample from a control subject having a non-metastasized breast tumor or no breast tumor. A significantly higher level of expression in the patient sample as compared to the level in the sample from the control subject is an indication that the breast cancer has metastasized or is likely to metastasize.

**[0019]** In another embodiment, the present invention includes a method for determining whether a patient has breast cancer that has metastasized to lymph nodes, or is likely to metastasize to lymph nodes, the method comprising

comparing the level of expression of a marker listed in Table 2 in a sample from the patient, and the level of expression in a sample from a control subject having a non-metastasized breast tumor or no breast tumor. A significantly higher level of expression in the patient sample as compared to the level in the sample from the control subject, is an indication that the patient is afflicted with metastatic breast cancer that has metastasized to lymph nodes, or is likely to metastasize to lymph nodes.

**[0020]** The invention also provides a method for predicting the clinical outcome of a breast cancer patient, comprising comparing the level of expression of at least one marker listed in Table 2 in a sample from the patient and the level of expression of the marker or markers in a sample for a control subject having a good clinical outcome (e.g., a former breast cancer patient having greater than five years of disease free survival level). A significantly higher level of expression in the patient sample as compared to the expression level in the sample from the control subject is an indication that the patient has a poor outcome (e.g., less than three years of disease free survival).

**[0021]** The invention also provides methods for assessing the efficacy of a therapy for inhibiting breast cancer in a patient. Such methods comprise comparing expression of at least one marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and expression of the marker or markers in a second sample obtained from the patient following provision of the portion of the therapy. A significantly lower level of expression of the marker or markers in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting breast cancer in the patient.

**[0022]** It will be appreciated that in these methods the "therapy" may be any therapy for treating breast cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy, such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in tumor burden.

**[0023]** In a preferred embodiment, the methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing expression of at least one marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent. A significantly lower level of expression of the marker or markers in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting breast cancer, in the patient. In certain embodiments, the first and second samples can be portions of a single sample obtained from the patient, or portions of pooled samples obtained from the patient.

**[0024]** The invention additionally provides a monitoring method for assessing progression of breast cancer in a patient, the method comprising:

**[0025]** detecting in a sample from the patient at a first time point, the expression of at least one marker of the invention;

**[0026]** repeating the detection of expression step at a subsequent time point in time; and

**[0027]** comparing the level of expression detected in the first and second detection steps, thereby monitoring the pro-

gression of breast cancer in the patient. A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the breast cancer has progressed in the patient, whereas a significantly lower level of expression is an indication that the breast cancer has regressed. In one embodiment, the patient has undergone surgery to remove a tumor between the first point in time and the subsequent point in time.

**[0028]** The invention moreover provides a test method for selecting a candidate composition for inhibiting breast cancer in a patient. This method comprises the steps of:

**[0029]** obtaining a sample comprising cancer cells from the patient;

**[0030]** separately maintaining at least one sample comprising cancer cells from the patient in the presence of at least one test composition;

**[0031]** comparing expression of at least one marker of the invention in each of the aliquots; and

**[0032]** selecting a test composition as a candidate composition for inhibition of breast cancer where the composition significantly reduces the level of expression of at least one marker of the invention in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

**[0033]** The invention additionally provides a test method of assessing the breast carcinogenic potential of a compound. This method comprises the steps of: maintaining separate aliquots of breast cells in the presence and absence of a compound; and comparing expression of a marker of the invention in each of the aliquots. A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses breast carcinogenic potential.

**[0034]** In addition, the invention further provides a method of inhibiting breast cancer in a patient. This method comprises the steps of:

**[0035]** obtaining a sample comprising cancer cells from a patient;

**[0036]** separately maintaining at least one sample comprising cancer cells from a patient in the presence of a test composition;

**[0037]** comparing expression of a marker of the invention in each of the aliquots;

**[0038]** identifying a composition as an inhibitor of breast cancer where the composition significantly lowers the level of expression of a marker of the invention in the aliquot containing the composition relative to the levels of expression of the marker in the presence of the other compositions; and

**[0039]** administering to the patient at least one of the compositions which are identified as an inhibitor of breast cancer.

**[0040]** According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

**[0041]** the corresponding marker protein (e.g., a protein having any one of the sequences of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID

NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96) or a fragment of the protein (e.g., by using a reagent, such as an antibody, an antibody derivative, an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment);

**[0042]** the corresponding marker nucleic acid (e.g., a nucleotide transcript having one of the sequences of the SEQ ID NOs (e.g., SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, and SEQ ID NO: 95), or a complement thereof), or a fragment of the nucleic acid (e.g., by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the sequence of any of the SEQ ID NOs (e.g., SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, and SEQ ID NO: 95)), or a complement thereof, or a metabolite which is produced directly (i.e., catalyzed) or indirectly by the corresponding marker protein.

**[0043]** According to the invention, any of the aforementioned methods may be performed using or detecting a plurality (e.g., 2, 3, 5, or 10 or more) of breast cancer markers, including a combination of the provided markers of the invention with additional breast cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with breast cancer. A significantly altered (i.e., increased or decreased as specified in the described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with breast cancer. For all of

the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

**[0044]** In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (e.g., a protein having the sequence of any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (e.g., a protein having the sequence of any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a fragment of the protein.

**[0045]** In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with a breast tumor. In another aspect, the kit may be used for assessing whether a patient is at risk of developing a breast tumor. The kit comprises a reagent for assessing expression of at least one marker of the invention. Yet another embodiment provides a kit which may be used for assessing whether a patient is afflicted with an aggressive breast tumor. The kit comprises a reagent for assessing expression of at least one marker of the invention. In another embodiment, the invention provides a kit for assessing the suitability of a chemical or biologic agent for inhibiting breast cancer in a patient. Such a kit comprises reagents for assessing expression of at least one marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention pro-

vides kits for assessing the presence of breast cancer cells or treating breast cancers. Such kits may comprise an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

**[0046]** In an additional embodiment, the invention provides a kit for assessing the presence of breast cancer cells, wherein the kit comprises at least one nucleic acid probe that binds specifically with at least one marker nucleic acid or a fragment of the nucleic acid. The kit may further comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

**[0047]** In a further aspect, the invention relates to methods for treating a patient afflicted with breast cancer or at risk of developing breast cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of at least one marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having the sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96, or a fragment of the protein.

**[0048]** It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known breast cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than breast cancer.

**[0049]** In another aspect the invention features nucleic acid molecules which encode marker proteins or marker polypeptides, e.g., a biologically active portion of the marker protein. In a preferred embodiment, the isolated nucleic acid molecules encode marker polypeptides having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48,

SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96. In other embodiments, the invention provides isolated marker nucleic acid molecules having the nucleotide sequences shown in any one selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, or SEQ ID NO: 95. In still other embodiments, the invention provides nucleic acid molecules that are substantially identical (e.g., naturally occurring allelic variants) to the nucleotide sequences shown in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, or SEQ ID NO: 95. In other embodiments, the invention provides nucleic acid molecules which hybridize under stringent hybridization conditions as described herein to nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, and SEQ ID NO: 95, wherein the nucleic acid encodes a full length marker protein or an active fragment thereof.

**[0050]** In a related aspect, the invention further provides nucleic acid constructs which include marker nucleic acid molecules described herein. In certain embodiments, the nucleic acid molecules of the invention are operatively linked to native or heterologous regulatory sequences. Also included

are vectors and host cells containing marker nucleic acid molecules of the invention e.g., vectors and host cells suitable for producing polypeptides.

**[0051]** In another related aspect, the invention provides nucleic acid fragments suitable as primers or hybridization probes for the detection of marker-encoding nucleic acids.

**[0052]** In still another related aspect, isolated nucleic acid molecules that are antisense to a marker encoding nucleic acid molecule are provided.

**[0053]** In other embodiments, the invention provides marker polypeptides, e.g., marker polypeptides having the amino acid sequences shown in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96; an amino acid sequence that is substantially identical to the amino acid sequences shown in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96; or amino acid sequences encoded by nucleic acid molecules having a nucleotide sequence which hybridizes under a stringent hybridization condition as described herein to nucleic acid molecules comprising the nucleotide sequences of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, and SEQ ID NO: 95, wherein the nucleic acid encodes a full length marker protein or an active fragment thereof.

**[0054]** In a related aspect, the invention further provides protein or peptide constructs which include polypeptide molecules described herein. In certain embodiments, the marker polypeptides or fragments of the invention are operatively

linked to native or heterologous non-marker polypeptide sequences to form fusion protein sequences.

**[0055]** In yet another aspect, the invention features antibodies and antigen-binding fragments thereof, that react with, or more preferably specifically or selectively bind marker polypeptides.

#### DETAILED DESCRIPTION OF THE INVENTION

**[0056]** The invention relates to newly discovered breast cancer markers set forth in Table 1, associated with the cancerous state of breast cells. It has been discovered that a higher than normal level of expression of any of these markers or combination of these markers correlates with breast cancer in a patient. Additionally, the invention relates to newly discovered breast cancer markers set forth in Table 2, associated with the cancerous state of breast cells. It has been discovered that a higher than normal level of expression of any of these markers or combination of these markers correlates with aggressiveness of breast cancer in a patient. Methods are provided for detecting the presence of breast cancer in a sample, the absence of breast cancer in a sample, the stage of breast cancer, assessing whether a breast cancer has metastasized, predicting the likely clinical outcome of a breast cancer patient, and with other characteristics of breast cancer that are relevant to prevention, diagnosis, characterization, and therapy of breast cancer in a patient. Methods of treating breast cancer are also provided.

**[0057]** Table 1 lists markers of the invention which are over-expressed in breast cancer patient samples compared to non-breast cancer patient samples (e.g., non-breast cancer patient samples, non-cancerous breast cells, other non-breast cancer patient samples). Table 1 lists markers particularly useful in screening for the presence of breast cancer (“screening markers”). Table 2 lists markers of the invention, which are over-expressed in poor outcome breast cancer patient samples compared to normal samples (e.g., good outcome breast cancer patient samples, non-breast cancer patient samples, non-cancerous breast cells). Table 2 lists markers particularly useful in assessing the stage of the breast cancer (“staging markers”). Table 1 and Table 2 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each marker, as well as the location of the protein coding sequence within the cDNA sequence. Tables 1 identifies markers of the invention (SEQ ID NOS:1-66) and Table 2 identifies markers of the invention (SEQ ID NOS: 67-96), which are designated with a name (“Marker”), the name the gene is commonly known by, if applicable (“Gene Name”), the Sequence Listing identifier of the cDNA sequence of the nucleotide transcript encoded by or corresponding to the marker (“SEQ ID NO (nts)”), the Sequence Listing identifier of the amino acid sequence of the protein encoded by the nucleotide transcript (“SEQ ID NO (AAs)”), and the location of the protein coding sequence within the cDNA sequence (“CDS”).

TABLE 1

| Breast Cancer Screening Markers |                                                                   |                 |                     |
|---------------------------------|-------------------------------------------------------------------|-----------------|---------------------|
| Marker                          | Gene Name                                                         | SEQ ID NO (nts) | SEQ ID NO (AAs) CDS |
| M196A                           | BCMP11: breast cancer membrane protein 11, variant 1              | 1               | 2 48 ... 548        |
| M725                            | BCMP11: breast cancer membrane protein 11, variant 2              | 3               | 4 49 ... 501        |
| M726                            | BCMP11: breast cancer membrane protein 11, variant 3              | 5               | 6 98 ... 412        |
| M727                            | BCMP11: breast cancer membrane protein 11, variant 4              | 7               | 8 49 ... 465        |
| M156                            | CXCL9: chemokine (C-X-C motif) ligand 9                           | 9               | 10 40 ... 417       |
| M419                            | CXCL10: chemokine (C-X-C motif) ligand 10                         | 11              | 12 67 ... 363       |
| M728                            | DNAJC1: DNAJ (hsp40) homolog, subfamily C, member 1, variant 1    | 13              | 14 244 ... 1152     |
| M729                            | DNAJC1: DNAJ (hsp40) homolog, subfamily C, member 1, variant 2    | 15              | 16 244 ... 1134     |
| M111                            | DNAJC1: DNAJ (hsp40) homolog, subfamily C, member 1, variant 3    | 17              | 18 108 ... 1772     |
| M428A                           | FLJ22774: hypothetical protein FLJ22774                           | 19              | 20 528 ... 3053     |
| M149A                           | LIV-1: LIV-1 protein, estrogen regulated, variant 1               | 21              | 22 282 ... 2549     |
| M730                            | LIV-1: LIV-1 protein, estrogen regulated, variant 2               | 23              | 24 309 ... 1751     |
| M158A                           | MMP11: matrix metalloproteinase 11 (stromelysin 3)                | 25              | 26 23 ... 1489      |
| M165A                           | NPY1R: neuropeptide Y receptor Y1, variant 1                      | 27              | 28 272 ... 1426     |
| M731                            | NPY1R: neuropeptide Y receptor Y1, variant 2                      | 29              | 30 241 ... 1005     |
| M732                            | NPY1R: neuropeptide Y receptor Y1, variant 3                      | 31              | 32 272 ... 700      |
| M235                            | NY-BR-1: breast cancer antigen NY-BR-1                            | 33              | 34 100 ... 4125     |
| M56A                            | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 1 | 35              | 36 12 ... 2522      |
| M733                            | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 2 | 37              | 38 12 ... 2438      |
| M734                            | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 3 | 39              | 40 12 ... 2441      |
| M735                            | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 4 | 41              | 42 12 ... 2357      |
| M491A                           | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 5 | 43              | 44 12 ... 2351      |
| M736                            | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 6 | 45              | 46 12 ... 2267      |
| M737                            | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 7 | 47              | 48 12 ... 2261      |

TABLE 1-continued

| <u>Breast Cancer Screening Markers</u> |                                                                                  |                 |                 |             |
|----------------------------------------|----------------------------------------------------------------------------------|-----------------|-----------------|-------------|
| Marker                                 | Gene Name                                                                        | SEQ ID NO (nts) | SEQ ID NO (AAs) | CDS         |
| M738                                   | OSF-2: osteoblast specific factor 2 (fasciclin I-like), variant 8                | 49              | 50              | 12 ... 2177 |
| M562                                   | PIP: prolactin-induced protein                                                   | 51              | 52              | 37 ... 477  |
| M96A                                   | SCUBE2: signal peptide, CUB domain, EGF-like 2, variant 1                        | 53              | 54              | 81 ... 3077 |
| M739                                   | SCUBE2: signal peptide, CUB domain, EGF-like 2, variant 2                        | 55              | 56              | 81 ... 2837 |
| M740                                   | SCUBE2: signal peptide, CUB domain, EGF-like 2, variant 3                        | 57              | 58              | 81 ... 2699 |
| M741                                   | SCUBE2: signal peptide, CUB domain, EGF-like 2, variant 4                        | 59              | 60              | 81 ... 3164 |
| M242                                   | TFF1: trefoil factor 1 (breast cancer, estrogen-inducible sequence expressed in) | 61              | 62              | 41 ... 295  |
| M716                                   | WFDC2: WAP four-desulfide core domain 2, variant 1                               | 63              | 64              | 28 ... 402  |
| M717                                   | WFDC2: WAP four-desulfide core domain 2, variant 2                               | 65              | 66              | 67 ... 288  |

TABLE 2

| <u>Breast Cancer Staging Markers</u> |                                                                                                                                      |                 |                 |              |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|--------------|
| Marker                               | Gene Name                                                                                                                            | SEQ ID NO (nts) | SEQ ID NO (AAs) | CDS          |
| M672A                                | ASS: argininosuccinate synthetase                                                                                                    | 67              | 68              | 81 ... 1319  |
| M675A                                | CAB2: hypothetical protein MGC9753                                                                                                   | 69              | 70              | 18 ... 980   |
| M367                                 | CD24: CD24 antigen (small cell lung carcinoma cluster 4 antigen)                                                                     | 71              | 72              | 57 ... 299   |
| M514                                 | DARPP-32: dopamine and cAMP regulated phosphoprotein, (PPP1R1B: protein phosphatase 1, regulatory (inhibitor) subunit 1B), variant 1 | 73              | 74              | 236 ... 742  |
| M708                                 | DARPP-32: dopamine and cAMP regulated phosphoprotein, (PPP1R1B: protein phosphatase 1, regulatory (inhibitor) subunit 1B), variant 2 | 75              | 76              | 468 ... 1082 |
| M709                                 | FACL2: fatty-acid-Coenzyme A ligase, long-chain 2, variant 1                                                                         | 77              | 78              | 124 ... 2220 |
| M710                                 | FACL2: fatty-acid-Coenzyme A ligase, long-chain 2, variant 2                                                                         | 79              | 80              | 188 ... 2284 |
| M495                                 | GSTP1: glutathione S-transferase pi                                                                                                  | 81              | 82              | 30 ... 662   |
| M674                                 | HN1: hematological and neurological expressed 1                                                                                      | 83              | 84              | 104 ... 568  |
| M234A                                | MGC14832: hypothetical protein MGC14832                                                                                              | 85              | 86              | 8 ... 355    |
| M408                                 | NDRG1: N-myc downstream regulated protein                                                                                            | 87              | 88              | 111 ... 1295 |
| M711                                 | ORMDL3: ORM1-like 3 ( <i>S. cerevisiae</i> )                                                                                         | 89              | 90              | 301 ... 762  |
| M678A                                | PSMB9: proteasome subunit, beta type, 9                                                                                              | 91              | 92              | 52 ... 711   |
| M421A                                | SERHL: kraken-like                                                                                                                   | 93              | 94              | 103 ... 1047 |
| M185A                                | SLPI: secretory leukocyte protease inhibitor (antileukoproteinase)                                                                   | 95              | 96              | 23 ... 421   |

## DEFINITIONS

**[0058]** As used herein, each of the following terms has the meaning associated with it in this section.

**[0059]** The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

**[0060]** A “marker” is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A “marker nucleic acid” is a nucleic acid (e.g., mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (e.g., cDNA) comprising the entire or a partial sequence of any of

SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, or SEQ ID NO: 95 or the complement of such a sequence. The marker nucleic acids also include RNA

comprising the entire or a partial sequence of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 73, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, SEQ ID NO: 81, SEQ ID NO: 83, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 89, SEQ ID NO: 91, SEQ ID NO: 93, or SEQ ID NO: 95 or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A “marker protein” is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the entire or a partial sequence of any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96. The terms “protein” and “polypeptide” are used interchangeably.

**[0061]** A “marker set” is a group of more than one marker.

**[0062]** The term “probe” refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

**[0063]** “Breast cancer” as used herein includes carcinomas, (e.g., carcinoma in situ, invasive carcinoma, metastatic carcinoma) and pre-malignant conditions.

**[0064]** A “breast-associated” body fluid is a fluid which, when in the body of a patient, contacts or passes through breast cells or into which cells, nucleic acids or proteins shed from breast cells are capable of passing. Exemplary breast-associated body fluids include blood fluids, lymph, cystic fluid, and nipple aspirates.

**[0065]** A “sample” or “patient sample” comprises cells obtained from the patient, e.g., a lump biopsy, body fluids including blood fluids, lymph and cystic fluids, as well as nipple aspirates. In a further embodiment, the patient sample is in vivo.

**[0066]** The “normal” level of expression of a marker is the level of expression of the marker in breast cells of a human subject or patient not afflicted with breast cancer.

**[0067]** An “over-expression” or “significantly higher level of expression” of a marker refers to an expression level in a

test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (e.g., sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

**[0068]** A “significantly lower level of expression” of a marker refers to an expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (e.g., sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

**[0069]** As used herein, the term “promoter/regulatory sequence” means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

**[0070]** A “constitutive” promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

**[0071]** An “inducible” promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

**[0072]** A “tissue-specific” promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

**[0073]** A “transcribed polynucleotide” or “nucleotide transcript” is a polynucleotide (e.g., an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (e.g., splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

**[0074]** “Complementary” refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds (“base pairing”) with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a

residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

**[0075]** “Homologous” as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

**[0076]** A molecule is “fixed” or “affixed” to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (e.g., standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

**[0077]** As used herein, a “naturally-occurring” nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found in nature.

**[0078]** A cancer is “inhibited” if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, breast cancer is also “inhibited” if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

**[0079]** A kit is any manufacture (e.g., a package or container) comprising at least one reagent, e.g., a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

**[0080]** “Proteins of the invention” encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

**[0081]** Unless otherwise specified herewithin, the terms “antibody” and “antibodies” broadly encompass naturally-occurring forms of antibodies (e.g., IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an

antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

**[0082]** The present invention is based, in part, on newly identified markers which are over-expressed in breast cancer cells as compared to their expression in normal (i.e., non-cancerous) breast cells. The enhanced expression of one or more of these markers in breast cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of breast cells (e.g., cells obtained from a human, cultured human cells, archived or preserved human cells and in vivo cells) as well as treating patients afflicted with breast cancer.

**[0083]** The compositions, kits, and methods of the invention have the following uses, among others:

**[0084]** assessing the status of breast cancer in a human patient;

**[0085]** assessing the stage of breast cancer in a human patient;

**[0086]** assessing the grade of breast cancer in a patient;

**[0087]** assessing the benign or malignant nature of breast cancer in a patient;

**[0088]** assessing the metastatic potential of breast cancer in a patient;

**[0089]** determining if breast cancer has metastasized to lymph nodes;

**[0090]** predicting the clinical outcome of a breast cancer patient;

**[0091]** assessing whether a patient is afflicted with breast cancer;

**[0092]** assessing the histological type of neoplasm associated with breast cancer in a patient;

**[0093]** making antibodies, antibody fragments or antibody derivatives that are useful for treating breast cancer and/or assessing whether a patient is afflicted with breast cancer;

**[0094]** assessing the presence of breast cancer cells;

**[0095]** assessing the efficacy of one or more test compounds for inhibiting breast cancer in a patient;

**[0096]** assessing the efficacy of a therapy for inhibiting breast cancer in a patient;

**[0097]** monitoring the progression of breast cancer in a patient;

**[0098]** selecting a composition or therapy for inhibiting breast cancer in a patient;

**[0099]** treating a patient afflicted with breast cancer;

**[0100]** inhibiting breast cancer in a patient;

**[0101]** assessing the breast carcinogenic potential of a test compound; and

**[0102]** preventing the onset of breast cancer in a patient at risk for developing breast cancer.

**[0103]** The invention thus includes a method of assessing breast cancer cells in a patient afflicted with breast cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, e.g., a non-breast cancer sample or a non-cancer, normal sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level of expression is an indication that the patient is afflicted with a breast tumor.

**[0104]** Additionally provided is a method of assessing aggressiveness of breast cancer cells in a patient afflicted with breast cancer. The method comprises comparing the level of expression of a marker of the invention (listed in Table 2) in a patient sample and the normal level of expression of the

marker in a control, e.g., a non-breast cancer sample or an indolent breast cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level of expression is an indication that the patient is afflicted with an aggressive breast tumor.

**[0105]** Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the sequences of the invention (e.g., SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 27, SEQ ID NO: 29, SEQ ID NO: 31, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 39, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 63, and SEQ ID NO: 65) or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the sequences of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96 are also provided by this invention.

**[0106]** As described herein, breast cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the breast cancer, others of these changes induce, maintain, and promote the cancerous state of breast cancer cells. Thus, breast cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

**[0107]** Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an RNA interference oligonucleotide or an antisense oligonucleotide can be provided to the breast cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the breast cancer cell with a peptide or an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit

expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit breast cancer cells of the patient.

**[0108]** Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in breast cancer cells and the level of expression of the same marker in normal breast cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal breast tissue.

**[0109]** It is recognized that certain marker proteins are secreted from breast cells (i.e., one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a breast-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred in vivo techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

**[0110]** It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human breast cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (e.g., using a labeled antibody which binds specifically with the protein).

**[0111]** The following is one example of a method which can be used to detect secretion of a protein: About  $8 \times 10^5$  293T cells are incubated at 37° C. in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO<sub>2</sub>, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424-54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-<sup>35</sup>S™ reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO<sub>2</sub> atmosphere described above and incubated at 37° C. for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris. The presence of the protein in the supernatant is an indication that the protein is secreted. Additional and alterna-

tive methods for detection of secreted proteins are known in the art and can be used in addition to, or alternative to this method.

**[0112]** It will be appreciated that patient samples containing breast cells may be used in the methods of the present invention. In these embodiments, the level of expression of the marker can be determined by assessing the amount (e.g., absolute amount or concentration) of the marker in a breast cell sample, e.g., breast biopsies obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e.g., nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, breast biopsies may also be subjected to post-collection preparative and storage techniques, e.g., fixation.

**[0113]** The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (i.e., including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (e.g., using a labeled antibody which binds specifically with a cell-surface domain of the protein).

**[0114]** Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

**[0115]** In a preferred embodiment, expression of a marker is assessed using an antibody (e.g., a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (e.g., an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {e.g., biotin-streptavidin}), or an antibody fragment (e.g., a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

**[0116]** In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (i.e., a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the

many known methods of detecting mutations or variants (e.g., single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

**[0117]** In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (e.g., at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (e.g., detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (e.g., a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

**[0118]** Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal breast cells and cancerous breast cells.

**[0119]** It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific breast cancers, as well as other cancers such as lung cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (i.e., 50% or more) or substantially all (i.e., 80% or more) of breast cancer. The compositions, kits, and methods of the invention are thus useful for characterizing the benign or malignant nature of breast tumors in patients.

**[0120]** Furthermore, it will be confirmed that certain of the markers of the invention are associated with breast cancer of various stages (i.e., stage 0, I, II, III, and IV breast cancers, as well as subclassifications IIA, IIB, IIIA, and IIIB, using the FIGO Stage Grouping system for primary carcinoma of the breast; (see Breast, In: *American Joint Committee on Cancer: AJCC Cancer Staging Manual*. Lippincott-Raven Publishers, 5th ed., 1997, pp. 171-180), of various histologic subtypes (e.g., serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal (Müllerian) mixed tumor, mesonephroid tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant breast tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington D.C.), and various grades (i.e., grade I {well differentiated}, grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered

expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of breast cancer in patients.

**[0121]** When the compositions, kits, and methods of the invention are used for characterizing the one or more of the stage, grade, histological type, and benign or malignant nature of breast tumors in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a breast tumor of the corresponding stage, grade, histological type, or benign or malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 80%).

**[0122]** When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (i.e., using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with breast cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, or 15, or more individual markers be used. Still further markers can be used to include a marker set wherein at least 20, 25, 30, 40, 50, or more individual markers are used.

**[0123]** In order to maximize the sensitivity of the compositions, kits, and methods of the invention (i.e., by interference attributable to cells of non-breast origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, e.g., normally not expressed in a non-breast tissue.

**[0124]** Only a small number of markers are known to be associated with breast cancers (e.g., BRCA1 and BRCA2). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

**[0125]** It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing breast cancer and their medical advisors. Patients recognized as having an enhanced risk of developing breast cancer include, for example, patients having a familial history of breast cancer,

patients identified as having a mutant oncogene (i.e., at least one allele), and patients of advancing age (i.e., women older than about 50 or 60 years).

**[0126]** The level of expression of a marker in normal (i.e., non-cancerous) breast tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is determined by assessing the level of expression of the marker in a portion of breast cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the breast cells which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of breast cancer in the patient, from archived patient samples, and the like.

**[0127]** The invention includes compositions, kits, and methods for assessing the presence of breast cancer cells in a sample (e.g., an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a paraffinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

**[0128]** The invention includes a kit for assessing the presence of breast cancer cells (e.g., in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (e.g., a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

**[0129]** The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (e.g., SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal breast cells, a sample of breast cancer cells, and the like.

**[0130]** The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether a patient is afflicted with breast cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (e.g., by purification from a cell in which it is expressed or by

transcription and translation of a nucleic acid encoding the protein or peptide in vivo or in vitro using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

**[0131]** The invention also includes a method of assessing the efficacy of a test compound for inhibiting breast cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of breast cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of breast cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit a breast cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (i.e., the level of expression for the marker in non-cancerous breast cells).

**[0132]** This method thus comprises comparing expression of a marker in a first breast cell sample and maintained in the presence of the test compound and expression of the marker in a second breast cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits breast cancer. The breast cell samples may, for example, be aliquots of a single sample of normal breast cells obtained from a patient, pooled samples of normal breast cells obtained from a patient, cells of a normal breast cell line, aliquots of a single sample of breast cancer cells obtained from a patient, pooled samples of breast cancer cells obtained from a patient, cells of a breast cancer cell line, or the like. In one embodiment, the samples are breast cancer cells obtained from a patient and one or more of a plurality of compounds known to be effective for inhibiting various breast cancers are tested in order to identify the compound which is likely to best inhibit the breast cancer in the patient.

**[0133]** This method may likewise be used to assess the efficacy of a therapy for inhibiting breast cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention, then the therapy is efficacious for inhibiting breast cancer. As above, if samples from a selected patient are used in this method, then alternative therapies can be assessed in vitro in order to select a therapy most likely to be efficacious for inhibiting breast cancer in the patient.

**[0134]** As described above, the cancerous state of human breast cells is correlated with changes in the levels of expres-

sion of the markers of the invention. The invention includes a method for assessing the human breast cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human breast cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human breast cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

**[0135]** Various aspects of the invention are described in further detail in the following subsections.

#### Isolated Nucleic Acid Molecules

**[0136]** One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, e.g., those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

**[0137]** An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

**[0138]** A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989).

**[0139]** A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to

standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

**[0140]** In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

**[0141]** Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

**[0142]** Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, e.g., detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

**[0143]** The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (e.g., protein having the sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96), and thus encode the same protein.

**[0144]** It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (e.g., the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic

variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (e.g., by affecting regulation or degradation).

**[0145]** As used herein, the phrase “allelic variant” refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

**[0146]** As used herein, the terms “gene” and “recombinant gene” refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

**[0147]** In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term “hybridizes under stringent conditions” is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6x sodium chloride/sodium citrate (SSC) at about 45° C., followed by one or more washes in 0.2xSSC, 0.1% SDS at 50-65° C.

**[0148]** In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at “non-essential” amino acid residues. A “non-essential” amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an “essential” amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration. Alternatively, amino acid residues that are conserved among the homologs of various species (e.g., murine and human) may be essential for activity and thus would not be likely targets for alteration.

**[0149]** Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ

in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

**[0150]** An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

**[0151]** The present invention encompasses antisense nucleic acid molecules, i.e., molecules which are complementary to a sense nucleic acid of the invention, e.g., complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (i.e., anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, e.g., all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions (“5' and 3' untranslated regions”) are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

**[0152]** An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used

to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N-6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methyl-ester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

**[0153]** The antisense nucleic acid molecules of the invention are typically administered to a subject or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into a breast-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

**[0154]** An antisense nucleic acid molecule of the invention can be an  $\alpha$ -anomeric nucleic acid molecule. An  $\alpha$ -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\alpha$ -units, the strands run parallel to each other (Gaultier et al., 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue et al., 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al., 1987, *FEBS Lett.* 215:327-330).

**[0155]** The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead

ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech et al. U.S. Pat. No. 4,987,071; and Cech et al. U.S. Pat. No. 5,116,742). Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, e.g., Bartel and Szostak, 1993, *Science* 261:1411-1418).

**[0156]** The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (e.g., the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

**[0157]** In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup et al., 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996), supra; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

**[0158]** PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup (1996), supra; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, supra; Perry-O'Keefe et al., 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

**[0159]** In another embodiment, PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA

portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, supra). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), supra, and Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl) amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al., 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al., 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Petersen et al., 1975, *Bioorganic Med. Chem. Lett.* 5:1119-11124).

**[0160]** In other embodiments, the oligonucleotide can include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaître et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, e.g., PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, e.g., Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

**[0161]** The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Pat. No. 5,876,930.

#### Isolated Proteins and Antibodies

**[0162]** One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to

recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

**[0163]** An “isolated” or “purified” protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language “substantially free of cellular material” includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a “contaminating protein”). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

**[0164]** Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

**[0165]** Preferred marker proteins are encoded by nucleotide sequences encoding proteins comprising the sequence of any one of: SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 76, SEQ ID NO: 78, SEQ ID NO: 80, SEQ ID NO: 82, SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96. Other useful proteins are substantially identical (e.g., at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

**[0166]** To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity=# of identical positions/total # of positions (e.g., overlapping positions)×100). In one embodiment the two sequences are the same length.

**[0167]** The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score=50, wordlength=3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., BLASTX and BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a k-tuple value of 2.

**[0168]** The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

**[0169]** The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a “chimeric protein” or “fusion protein” com-

prises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (i.e., a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

**[0170]** One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

**[0171]** In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel et al., ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, Calif.). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook et al., supra) and the protein A secretory signal (Pharmacia Biotech; Piscataway, N.J.).

**[0172]** In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction in vivo. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (e.g., promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of the marker protein with ligands.

**[0173]** Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, e.g., Ausubel et al., supra). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

**[0174]** A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typi-

cally characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (i.e., the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

**[0175]** The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, e.g., discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

**[0176]** Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang, 1983, *Tetrahedron* 39:3; Itakura et al., 1984, *Annu. Rev. Biochem.* 53:323; Itakura et al., 1984, *Science* 198:1056; Ike et al., 1983 *Nucleic Acid Res.* 11:477).

**[0177]** In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest

with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

**[0178]** Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave et al., 1993, *Protein Engineering* 6(3):327-331).

**[0179]** Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (i.e., such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, e.g., an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, e.g., a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')<sub>2</sub> fragments.

**[0180]** An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, e.g., hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

**[0181]** An immunogen typically is used to prepare antibodies by immunizing a suitable (i.e., immunocompetent) sub-

ject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

**[0182]** The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

**[0183]** Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (see Kozbor et al., 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole et al., pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan et al. ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

**[0184]** Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Pat. No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum.*

*Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

**[0185]** The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Pat. No. 4,816,567; and Boss et al., U.S. Pat. No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an antigen binding site and consist of a single polypeptides. They can be produced by techniques known in the art, for example using methods described in Ladner et. al U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird et al., (1988) *Science* 242:423-426; Whitlow et al., (1991) *Methods in Enzymology* 2:1-9; Whitlow et al., (1991) *Methods in Enzymology* 2:97-105; and Huston et al., (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, U.S. Pat. No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Whitlow et al., (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

**[0186]** Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Pat. No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Pat. No. 4,816,567; European Patent Application 125,023; Better et al. (1988) *Science* 240:1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al. (1987) *J. Immunol.* 139:3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al. (1987) *Cancer Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi et al. (1986) *Bio/Techniques* 4:214; U.S. Pat. No. 5,225,539; Jones et al. (1986) *Nature* 321:552-525; Verhoeyan et al. (1988) *Science* 239:1534; and Beidler et al. (1988) *J. Immunol.* 141:4053-4060.

**[0187]** More particularly, humanized antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal antibodies directed against the antigen can be

obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Pat. No. 5,625,126; U.S. Pat. No. 5,633,425; U.S. Pat. No. 5,569,825; U.S. Pat. No. 5,661,016; and U.S. Pat. No. 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, Calif.), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

**[0188]** Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers et al., 1994, *Bio/technology* 12:899-903).

**[0189]** The antibodies of the invention can be isolated after production (e.g., from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

**[0190]** In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

**[0191]** An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques,

such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (e.g., in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (e.g., in a breast-associated body fluid) as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase,  $\beta$ -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

**[0192]** Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having a breast cancer. In another preferred embodiment, antibodies that bind specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrocorticosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thiopepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

**[0193]** The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Pat. No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diph-

theria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

**[0194]** Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Amon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

**[0195]** Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

**[0196]** The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In one embodiment, the pharmaceutical composition comprises an antibody of the invention, a therapeutic moiety, and a pharmaceutically acceptable carrier.

#### Recombinant Expression Vectors and Host Cells

**[0197]** Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of

vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

**[0198]** The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol. 185, Academic Press, San Diego, Calif. (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

**[0199]** The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (e.g., *E. coli*) or eukaryotic cells (e.g., insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

**[0200]** Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification.

Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

**[0201]** Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann et al., 1988, *Gene* 69:301-315) and pET 11d (Studier et al., p. 60-89, In *Gene Expression Technology Methods in Enzymology* vol. 185, Academic Press, San Diego, Calif., 1991). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

**[0202]** One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, Calif., 1990). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada et al., 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

**[0203]** In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari et al., 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz et al., 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and pPicZ (Invitrogen Corp, San Diego, Calif.).

**[0204]** Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith et al., 1983, *Mol. Cell. Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

**[0205]** In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman et al., 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook et al., *supra*.

**[0206]** In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al., 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji et al., 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund et al., 1985, *Science* 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss, 1990, *Science* 249:374-379) and the  $\alpha$ -fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

**[0207]** The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub et al., 1986, *Trends in Genetics*, Vol. 1(1).

**[0208]** Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

**[0209]** A host cell can be any prokaryotic (e.g., *E. coli*) or eukaryotic cell (e.g., insect cells, yeast or mammalian cells).

**[0210]** Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for trans-

forming or transfecting host cells can be found in Sambrook, et al. (supra), and other laboratory manuals.

**[0211]** For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker will survive, while the other cells die).

**[0212]** A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further comprises isolating the a marker protein or a segment thereof from the medium or the host cell.

**[0213]** The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

**[0214]** A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene.

A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Pat. Nos. 4,736,866 and 4,870,009, U.S. Pat. No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

**[0215]** To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a “knock out” vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, e.g., Thomas and Capecchi, 1987, *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, e.g., Li et al., 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see, e.g., Bradley, *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

**[0216]** In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example

of such a system is the cre/loxP recombinase system of bacteriophage P1. For a description of the cre/loxP recombinase system, see, e.g., Lakso et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman et al., 1991, *Science* 251:1351-1355). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of “double” transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

**[0217]** Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut et al. (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

#### Pharmaceutical Compositions

**[0218]** The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as “active compounds”) of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language “pharmaceutically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

**[0219]** The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

**[0220]** The invention also provides methods (also referred to herein as “screening assays”) for identifying modulators, i.e., candidate or test compounds or agents (e.g., peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (e.g., stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (e.g., peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

**[0221]** The test compounds of the present invention may be obtained from any available source, including systematic

libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, e.g., Zuckermann et al., 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

**[0222]** Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop et al. (1994) *J. Med. Chem.* 37:1233.

**[0223]** Libraries of compounds may be presented in solution (e.g., Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, U.S. Pat. No. 5,223,409), plasmids (Cull et al., 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla et al., 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, supra.).

**[0224]** In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (e.g., marker substrates) can be labeled with  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^3\text{H}$ , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

**[0225]** In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion thereof. In all likelihood, the protein encoded by or corresponding to the marker can, in vivo, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids.

For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker "substrate".

**[0226]** One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural in vivo binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Pat. No. 5,283,317; Zervos et al., 1993, *Cell* 72:223-232; Madura et al., 1993, *J. Biol. Chem.* 268:12046-12054; Bartel et al, 1993, *Biotechniques* 14:920-924; Iwabuchi et al., 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

**[0227]** The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, in vivo, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

**[0228]** In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (e.g., affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is a breast cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

**[0229]** The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and

absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

**[0230]** The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the marker proteins and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, i.e., by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, e.g., compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

**[0231]** In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

**[0232]** In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, Mo.) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (e.g., physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be disso-

ciated from the matrix, and the level of marker binding or activity determined using standard techniques.

**[0233]** Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

**[0234]** In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

**[0235]** In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

**[0236]** In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A. P., *Trends Biochem Sci* 1993 August; 18(8): 284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange

chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, 1998, *J. Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.*, 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, e.g., Ausubel et al (eds.), In: *Current Protocols in Molecular Biology*, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, e.g., Ausubel et al (eds.), In: *Current Protocols in Molecular Biology*, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

[0237] Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, e.g., Lakowicz et al., U.S. Pat. No. 5,631,169; Stavrianopoulos et al., U.S. Pat. No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (e.g., marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (e.g., marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

[0238] In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

[0239] In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, e.g., in a whole animal model for cellular transformation and/or tumorigenesis.

[0240] This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., an marker modulating agent, an antisense marker nucleic acid molecule, an marker-specific antibody, or an marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

[0241] It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate

doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (e.g., a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

**[0242]** A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

**[0243]** Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

**[0244]** Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

**[0245]** Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

**[0246]** Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

**[0247]** For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

**[0248]** Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

**[0249]** The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

**[0250]** In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including

liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

**[0251]** It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

**[0252]** For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration. A method for lipidation of antibodies is described by Cruikshank et al. (1997) *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193.

**[0253]** The invention also provides vaccine compositions for the prevention and/or treatment of breast cancer. The invention provides breast cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune response against the breast cancer. The invention also provides breast cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune response.

**[0254]** In one embodiment, a breast cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of breast cancer. In another embodiment, a breast cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of breast cancer.

**[0255]** By way of example, a breast cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of breast cancer in a subject by administering the vaccine by a variety of routes, e.g., intradermally, subcutaneously, or intramuscularly. In addition, the breast cancer vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow release of such materials into the body. The breast cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

**[0256]** In another embodiment, a breast cancer vaccine comprised of an expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune response. In addition, the breast cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

**[0257]** The marker nucleic acid molecules can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Pat. No. 5,328,470), or by stereotactic injection (see, e.g., Chen et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

**[0258]** The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

#### Predictive Medicine

**[0259]** The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing breast cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

**[0260]** Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds administered either to inhibit breast cancer or to treat or prevent any other disorder {i.e., in order to understand any breast carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

#### Diagnostic Assays

**[0261]** An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (e.g., a breast associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (e.g., mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of mRNA include Northern hybridizations and in situ

hybridizations. In vitro techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. In vitro techniques for detection of genomic DNA include Southern hybridizations. Furthermore, in vivo techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

**[0262]** A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

**[0263]** For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

**[0264]** There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

**[0265]** Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

**[0266]** In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (e.g., by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

**[0267]** In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

**[0268]** It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for

example, Lakowicz et al., U.S. Pat. No. 5,631,169; Stavrianopoulos, et al., U.S. Pat. No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (e.g., using a fluorimeter).

**[0269]** In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, e.g., Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345 and Szabo et al., 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

**[0270]** Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A. P., 1993, *Trends Biochem Sci.* 18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, e.g., Heegaard, N. H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D. S., and Tweed, S. A. *J Chromatogr B Biomed Sci Appl* 1997 Oct. 10; 699(1-2):499-525). Gel electrophoresis may also be

employed to separate complexed assay components from unbound components (see, e.g., Ausubel et al., ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

**[0271]** In a particular embodiment, the level of marker mRNA can be determined both by in situ and by in vitro formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA. For in vitro methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from breast cells (see, e.g., Ausubel et al., ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Pat. No. 4,843,155).

**[0272]** The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

**[0273]** In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

**[0274]** An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, e.g., by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Pat. No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained sequence replication (Guatelli et al., 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh et al., 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi et al., 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi et al., U.S. Pat. No. 5,854,033) or any other

nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked by the primers.

**[0275]** For in situ methods, mRNA does not need to be isolated from the breast cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the marker.

**[0276]** As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, e.g., a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, e.g., a patient sample, to another sample, e.g., a non-breast cancer sample, or between samples from different sources.

**[0277]** Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

**[0278]** Preferably, the samples used in the baseline determination will be from breast cancer or from non-breast cancer cells of breast tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is breast specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from breast cells provides a means for grading the severity of the breast cancer state.

**[0279]** In another embodiment of the present invention, a marker protein is detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or

a fragment or derivative thereof (e.g., Fab or F(ab')<sub>2</sub>) can be used. The term “labeled”, with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

**[0280]** Proteins from breast cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.).

**[0281]** A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether breast cells express a marker of the present invention.

**[0282]** In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

**[0283]** One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from breast cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

**[0284]** The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (e.g., a breast-associated body fluid such as a nipple aspirate). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing breast cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (e.g., an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

**[0285]** For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a marker protein; and, optionally, (2) a second,

different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

**[0286]** For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

#### Pharmacogenomics

**[0287]** The markers of the invention are also useful as pharmacogenomic markers. As used herein, a “pharmacogenomic marker” is an objective biochemical marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, e.g., McLeod et al. (1999) *Eur. J. Cancer* 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

**[0288]** Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

**[0289]** As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19

quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

**[0290]** Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

#### Monitoring Clinical Trials

**[0291]** Monitoring the influence of agents (e.g., drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for breast cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

#### Electronic Apparatus Readable Media and Arrays

**[0292]** Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

**[0293]** As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

**[0294]** As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

**[0295]** A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (e.g., text file or database) may be employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

**[0296]** By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

**[0297]** The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has breast cancer or a pre-disposition to breast cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has breast cancer or a pre-disposition to breast cancer and/or recommending a particular treatment for breast cancer or pre-breast cancer condition.

**[0298]** The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has breast cancer or a pre-disposition to breast cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has breast cancer or a pre-disposition to breast cancer, and/or recommending a particular treatment for the breast cancer or pre-breast cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

**[0299]** The present invention also provides in a network, a method for determining whether a subject has breast cancer or a pre-disposition to breast cancer associated with a marker, said method comprising the steps of receiving information

associated with the marker receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or breast cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a breast cancer or a pre-disposition to breast cancer. The method may further comprise the step of recommending a particular treatment for the breast cancer or pre-breast cancer condition.

**[0300]** The present invention also provides a business method for determining whether a subject has breast cancer, an aggressive breast tumor or a pre-disposition to breast cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or breast cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has breast cancer or a pre-disposition to breast cancer. The method may further comprise the step of recommending a particular treatment for the breast cancer or pre-breast cancer condition.

**[0301]** The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

**[0302]** In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression per se and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

**[0303]** In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of breast cancer, progression of breast cancer, and processes, such as cellular transformation associated with breast cancer.

**[0304]** The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example,

for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

**[0305]** The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

#### Surrogate Markers

**[0306]** The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, breast cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (e.g., with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (e.g., early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (e.g., an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate markers in the art include: Koomen et al. (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

**[0307]** The markers of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug in vivo. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic

marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda et al. U.S. Pat. No. 6,033,862; Hattis et al. (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

#### EXAMPLE 1

##### Identification of Breast Cancer Markers by cDNA and Tissue Microarrays

###### I. Materials and Methods

###### Sample Collection and RNA Preparation

**[0308]** Breast tissues were collected and snap frozen in liquid nitrogen. The histology and cellular composition of tissues were confirmed before RNA extraction was performed. Total RNA was extracted from the frozen tissues using Trizol Reagent (Invitrogen, San Diego, Calif.) followed by a secondary clean up step with Qiagen's RNeasy kit to increase RNA probe labeling efficiency (Qiagen, Valencia Calif.). Only RNA with a 28S/18S ribosomal RNA ratio of at least 1.0, calculated from ethidium staining of the RNA after electrophoresis on agarose gels, was used in this study.

###### cDNA Microarray Hybridization

**[0309]** cDNA microarrays containing 30,732 Unigene clones from Research Genetics (Huntsville, Ala.) were generated on nylon filters. A total of 4-6 ug of total RNA was used as template to generate radioactively labeled cDNA by reverse transcription with  $^{33}\text{P}$ -dCTP, oligo dT-30 primer and Superscript II Reverse Transcriptase (Life Technologies).  $^{33}\text{P}$ -labeled first strand cDNA was preannealed with cot-1 DNA and poly-dA 40-60 (Pharmacia, Peapack, N.J.) to reduce non-specific hybridization. Each filter was hybridized at 65° C. for 16 hours with approximately  $6 \times 10^6$  counts of labeled probe in a buffer containing 7% sodium dodecyl sulfate (SDS), 250 mM  $\text{Na}_3\text{PO}_4$  (pH 7.2), 1 mM EDTA, 0.5% Casein-Hammerstein and 0.1 mg/ml of denatured salmon sperm DNA. After the filters were washed with 4% and 1% SDS wash buffer (20 mM  $\text{Na}_3\text{PO}_4$  (pH 7.2), 1 mM EDTA and 4% or 1% SDS), they were exposed to Fuji Phosphorimager screens and scanned using a Fuji scanner BAS 2500. Spots were quantitated using an automated array analysis program, Grid Guru v1.0, developed at Millennium Pharmaceuticals, Inc.

###### Marker Scoring Algorithm and Data Analysis

**[0310]** To correct for differences in hybridization efficiency, the digitized data from each microarray filter was normalized by the median intensity of all spots on that filter. Both array-based and gene-based hierarchical clustering was performed and visualized using Stanford's Gene Cluster and Tree View software. Differentially expressed genes were ranked by calculating the Marker Score for each gene.

**[0311]** Samples were divided into control and tester groups for computation of Marker Score. The starting point for the Marker Score is average fold change (ratio) of the tester samples above the control samples. The score was designed to reflect both the degree of change (the expression ratio) and the number of tester samples showing differential expression, while not being dominated by a small fraction of tester samples with very high values. To reduce this "outlier" effect,

genes were treated with expression ratios greater than 10 as not meaningfully different from those with ratios of 10. This desired performance from a Marker Score was accomplished by transforming the tester:control expression ratio using an asymptotic compression function before taking the average fold-change across tester samples. A Marker Score has a value of 1 when the testers do not appear to be expressed more highly than the controls and a value greater than 1 otherwise. A Marker Score cannot exceed a value of 10 for any gene.

**[0312]** The Marker Score  $S_g$  for gene  $g$  is therefore computed as the average of the ratios of weighted intensities of the individual testers and a control level as follows:

$$S_g = (\sum S_{gs}) / N_{tester}$$

$S_{gs} = C(x_{gs} / (k + x_g^Q))$ , where  $S_{gs}$  represents the Marker Score for gene  $g$  and the sample  $s$ ,

$C(r)$  is the compression function  $C(r) = A(1 - e^{-r/A})$  for  $r \geq 1$ , and  $C(r) = 1$  for  $r < 1$ ,

$A$  is an upper asymptote on the fold-change value (we used 10),

$x_{gs}$  is the expression value of gene  $g$  on sample  $s$ ,

$x_g^Q$  is the  $Q$ th percentile of the control samples' expression value; typically  $Q = 50$ ,

$k$  is a constant reflecting the additive noise in the data, i.e., the fixed component of the variance in repeated measurements. A value of 0.25 was derived for this parameter from calibration experiments using microarray technology.

$N_{tester}$  is the number of tester samples

###### In Situ Hybridization of Tissue Microarrays

**[0313]** Formalin-fixed, paraffin embedded breast tissue microarrays were provided. Prehybridization treatment was performed with an automatic Tissue-Tek DRS 2000 Slide Stainer (Sakura, Torrance, Calif.) using a previously described protocol (Duncan, L. M., et al., 2001, *J. Clin. Oncol.* 19(2): 568-576). The breast tissues were deparaffinized, rehydrated and postfixed with 4% paraformaldehyde in PBS for 15 minutes. After washing with PBS, the tissue microarrays were digested with 2 ug/ml proteinase K at 37° C. for 15 minutes and again incubated with 4% paraformaldehyde/PBS for 10 minutes. Tissue sections were subsequently incubated with 0.2N HCL for 10 minutes, 0.25% acetic anhydride/0.1 mol/L triethanolamine for 10 minutes, and dehydrated with graded ethanol. Antisense probes were labeled with  $^{35}\text{S}$ -UTP in an in vitro transcription reaction (Riboprobe Combination System, Promega, Madison, Wis.) using 500 ng of linearized plasmid DNA derived from IMAGE clones. Hybridizations were performed at 50° C. for 18 hours using probes labeled at  $5 \times 10^7$  cpm/ml in 10 mM Tris-HCl (pH 7.6) buffer containing 50% formamide, 10% dextran sulfate, 1xDenhardt's solution, 0.6 M NaCl, 10 mM DTT, 0.25% SDS and 200 ug/ml tRNA. After hybridization, slides were washed with 5x standard saline citrate (SSC) at 50° C. for 10 minutes, 50% formamide/2xSSC at 50° C. for 30 minutes, 10 mM Tris-HCl (pH 7.6)/500 mM NaCl/1 mM EDTA (TNE) at 37° C. for 10 minutes, incubated in 10 ug/ml Rnase A in TNE at 37° C. for 30 minutes, washed in TNE at 37° C. for 10 minutes, incubated once in 2xSSC at 50° C. for 20 minutes, twice in 0.2xSSC at 50° C. for 20 minutes, and dehydrated with graded ethanol. Localization of mRNA transcripts was determined by dipping slides in Kodak NTB2 photoemulsion (Eastman Kodak, Rochester, N.Y.) and expos-

ing for 14-21 days at 4° C. The slides were counterstained using Myers hematoxylin and alcoholic eosin Y.

#### Gene Expression Analysis Using Quantitative PCR

**[0314]** Gene expression was measured by TAQMAN® quantitative PCR (Applied Biosystems) in cDNA prepared from normal and diseased (e.g., cancerous) human tissue samples. Briefly, total RNA was prepared from patient samples by a single step extraction method using TRIZOL Reagent according to the manufacturer's instructions (Invitrogen). Each RNA preparation was treated with DNase I (Ambion) at 37° C. for 1 hour. DNase I treatment was determined to be complete if the sample required at least 38 PCR amplification cycles to reach a threshold level of fluorescence using  $\beta$ -2 microglobulin as an internal amplicon reference (or 35 PCR amplification cycles for 18 s ribosome gene). The integrity of the RNA samples following DNase I treatment was confirmed by agarose gel electrophoresis and ethidium bromide staining. After phenol extraction cDNA was prepared from the sample using the Taqman Reverse Transcription Reagents following the manufacturer's instructions (Applied Biosystems). A negative control of RNA without reverse transcriptase was mock reverse transcribed for each RNA sample.

**[0315]** Probes were designed by PrimerExpress software (Applied Biosystems) based on the sequence of the specific genes and their related transcripts. Each target gene probe was labeled using FAM (6-carboxyfluorescein), and the 18 s reference probe was labeled with a different fluorescent dye, VIC. The differential labeling of the target gene and internal reference gene thus enabled measurement in same well. Primer and probes were checked for their sensitivity and specificity for each transcript of the specific gene. Forward and reverse primers and the probes for both 18 s and target gene were added to the TAQMAN® Universal PCR Master Mix (Applied Biosystems). Although the final concentration of primer and probe could vary, each was internally consistent within a given experiment. A typical experiment contained 100 nM of forward and reverse primers plus 200 nM probe for 18 s and 900 nM forward and reverse primers plus 250 nM probe for the target gene. TAQMAN® matrix experiments were carried out on an ABI PRISM 7700 Sequence Detection System (Applied Biosystems). The thermal cycler conditions were as follows: hold for 2 min at 50° C. and 10 min at 95° C., followed by two-step PCR for 40 cycles of 95° C. for 15 sec followed by 60° C. for 1 min.

**[0316]** The following method was used to quantitatively calculate gene expression in the various tissues relative to 18 s expression in the same tissue. The threshold cycle (Ct) value is defined as the cycle at which a statistically significant increase in fluorescence is detected. A lower Ct value is indicative of a higher mRNA concentration. The Ct value of the gene is normalized by subtracting the Ct value of the 18 s ribosome gene to obtain a  $\Delta$ Ct value using the following formula:  $\Delta$ Ct=Ct (target transcript)-Ct (18 s). Relative expression is then calculated using the arithmetic formula given by  $2^{-\Delta$ Ct.

## II. Results

### Screening Marker Selection

**[0317]** All of the markers listed in Table 1 were identified by transcription profiling as defined in the materials and methods section above using mRNA from a breast screening

panel consisting of patient samples of a "breast tumor pool" (3 breast tumor patient samples), a "breast normal pool" (3 normal breast epithelium patient samples), an "other normals pool" (one sample from normal heart, kidney, small intestine, spleen, white blood cells, lung, liver, brain, bone marrow and colon patient tissue samples) and an "others tumors pool" (4 cervical carcinoma, 5 colon tumor, 8 lung carcinoma patient samples of various types, 4 ovarian tumor samples, and 5 prostate tumor samples). Clones having expression of at least three-fold higher in at least 25% of breast tumors, compared to their expression breast normal, other normal or other tumors, were designated as breast tumor specific screening markers. These cDNA clones were selected to have their protein-encoding transcript sequences determined.

**[0318]** In order to determine the full-length protein-encoding transcripts for the selected cDNA clones, the sequence(s) of the selected clones were used to query the public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into protein-encoding transcripts. Alternative transcript analysis for all of the claimed markers was undertaken as follows.

**[0319]** Using existing mappings of known nucleotide sequences for any given marker gene to the human genome sequence and by additionally mapping novel nucleotide sequences for any given marker gene onto the human genome sequence (e.g., using resources like the "UCSC genome browser" or in-house resources of similar functionality in conjunction with algorithms like BLAT that allow a rapid and precise mapping of search sequences onto genomic sequence), the exon-intron structure of a marker gene was established, taking additionally into account EST sequences matching the same gene.

**[0320]** PCR primers were designed to amplify the coding sequence of a given marker gene from the tissue of interest and control samples. Any alternative 5' or 3' ends of a marker gene arising from this analysis with the potential to alter the coding sequence led to the design of an additional primer specific for this alternative end.

**[0321]** PCR products obtained with cDNA templates derived from breast tumor specimens were cloned into a plasmid vector and characterized by DNA sequence analysis. Typically, 96 clones were analyzed by restriction digestion and gel electrophoresis of the PCR products or by DNA sequence analysis.

**[0322]** Clones representative of alternative gene transcripts occurring at a frequency of 2% or greater were sequenced. The identification of protein sequence corresponding to these alternative transcripts was accomplished by the identification of the open reading frame (ORF) contained within a manually curated assembly (contig) based on all available sequences. The identified sequences are designated in Table 1 and the sequence listing.

**[0323]** Differential gene expression of genes with identified alternative transcripts was confirmed by TAQMAN® quantitative PCR (Applied Biosystems) in cDNA prepared from the patient tissue specimens. Gene specific TAQMAN® reagents which were sensitive for all transcripts identified for a given gene were prepared in certain instances (e.g., BCMP11, DNAJC1 and NPY1R). Additionally, splice-form specific TAQMAN® reagent sets were developed for each transcript of certain markers separately (e.g., M725, M726, M727, M111, M149, M730, M165A, M731, M732, M96A, M739, M740, M741, M716, M717). With one exception,

gene-specific as well as transcript-specific expression profiles demonstrating differential tumor-normal expression, with similar amplification efficiencies were found. In one case

within a manually curated assembly (contig) based on all available sequences. The identified protein sequences are designated in Table 2 and the sequence listing.

TABLE 3

| Breast Cancer Staging Marker Differential Expression |                                                                                                                           |                      |             |                      |             |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|----------------------|-------------|----------------------|-------------|
| Marker                                               | Gene Name                                                                                                                 | GOP<br>Pos/<br>Total | GOP<br>Freq | POP<br>Pos/<br>Total | POP<br>Freq |
| M672A                                                | ASS: argininosuccinate synthetase                                                                                         | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M675A                                                | CAB2: hypothetical protein MGC9753                                                                                        | 2 of 28              | 7.1%        | 3 of 37              | 8.1%        |
| M367                                                 | CD24: CD24 antigen (small cell lung carcinoma cluster 4 antigen)                                                          | 6 of 32              | 18.8%       | 16 of 38             | 42.1%       |
| M709                                                 | FACL2: fatty-acid-Coenzyme A ligase, long-chain 2                                                                         | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M495                                                 | GSTP1: glutathione S-transferase pi                                                                                       | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M674                                                 | HN1: hematological and neurological expressed 1                                                                           | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M234A                                                | MGC14832: hypothetical protein MGC14832                                                                                   | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M408                                                 | NDRG1: N-myc downstream regulated protein                                                                                 | 5 of 35              | 14.3%       | 12 of 39             | 30.8%       |
| M711                                                 | ORMDL3: ORM1-like 3 ( <i>S. cerevisiae</i> )                                                                              | 5 of 28              | 17.9%       | 13 of 35             | 37.1%       |
| M514                                                 | DARPP-32: dopamine and cAMP regulated phosphoprotein, (PPP1R1B: protein phosphatase 1, regulatory (inhibitor) subunit 1B) | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M678A                                                | PSMB9: proteasome subunit, beta type, 9                                                                                   | 0 of 25              | 0.0%        | 0 of 39              | 0.0%        |
| M421A                                                | SERHL: kraken-like                                                                                                        | 5 of 33              | 15.2%       | 9 of 37              | 24.3%       |
| M185A                                                | SLPI: secretory leukocyte protease inhibitor (antileukoproteinase)                                                        | 3 of 25              | 12.0%       | 4 of 36              | 11.1%       |

(M731, a NPY1R transcript), expression was not demonstrated with TAQMAN® PCR, presumably due to low abundance of this transcript.

#### Staging Marker Selection

**[0324]** All of the markers listed in Table 2 were identified by transcription profiling as defined in the materials and methods section using mRNA from 23 IDC node negative breast tumors with good outcome, defined as greater than five years of disease-free survival, and 16 IDC node negative breast tumors with poor clinical outcome, defined as less than three years of disease free survival. Clones having expression of at least three-fold higher in at least 25% of poor clinical outcome tumors, compared to their expression in good clinical outcome tumors, were designated as poor clinical outcome tumor specific markers. These cDNA clones were selected to have their protein-encoding transcript sequences determined.

**[0325]** Determination of the full-length protein encoding transcripts for selected cDNA clones was carried out as described above for the screening markers. The identified sequences are designated in Table 2 and the sequence listing. The differential gene expression of the identified alternative transcripts was confirmed by TAQMAN® quantitative PCR (Applied Biosystems) in cDNA prepared from patient tissue specimens from invasive ductal carcinoma (IDC) tumors with good outcome and poor outcome. Splice-form specific Taq-Man primers and probe reagent sets were developed for each transcript and similar amplification efficiencies were obtained with all reagent sets for each gene (see Table 3).

**[0326]** The identification of protein sequences corresponding to these alternative transcripts was accomplished by the identification of the open reading frame (ORF) contained

#### EXAMPLE 2

##### Gene Expression Analysis by End-Point PCR

##### I. Materials and Methods

**[0327]** Briefly, total RNA from different samples was pooled to be used as template to generate first strand cDNA. Equal amounts of each sample were included in the pool. The breast screening panel consisted of patient samples of a “breast tumor pool” (3 breast tumor patient samples), a “breast normal pool” (3 normal breast epithelium patient samples), an “other normals pool” (one sample from normal heart, kidney, small intestine, spleen, white blood cells, lung, liver, brain, bone marrow and colon patient tissue samples) and an “others tumors pool” (4 cervical carcinoma, 5 colon tumor, 8 lung carcinoma patient samples of various types, 4 ovarian tumor samples, and 5 prostate tumor samples) (see, e.g., Table 2). The breast staging panel consisted of patient samples of a “tumor good outcome pool” (4 adenocarcinoma patient samples), a “tumor poor outcome pool” (5 adenocarcinoma patient samples), a “breast normal pool” (4 normal breast epithelium patient samples), an “other normals pool” (one patient sample from normal heart, kidney, small intestine, spleen, white blood cells, lung, liver brain, bone marrow and colon) and an “others tumors pool” (cervical, colon, lung, ovarian and prostate tumors) (see, e.g., Table 3).

**[0328]** Total RNA was prepared from patient samples by a single step extraction method using TRIZOL Reagent according to the manufacturer's instructions (Invitrogen). Each RNA preparation was treated with DNase I (Ambion) at 37° C. for 1 hour. RNA from each patient sample was pooled into one of the four patient pools, e.g., breast normal pool, breast tumor pool, other normals pool, others tumors pool. ThermoScript RT-PCR System (Invitrogen, San Diego,

Calif.) was used to obtain cDNA from each of the five patient pools. Briefly, 1 µg RNA was denatured at 65° C. for 5 min with 1 µl of 50 µM oligo (dT)20 primer in a 10 µl volume according to the manufacturer's instructions. The reaction was terminated by incubation at 85° C. for 5 min. The final product was diluted with water to a final volume of 100 µl.

[0329] Gene specific primers were designed just outside the Open Reading Frame (as shown in Table 2 categories "Endpoint PCR Primer 1" and "Endpoint PCR Primer 2"). The PCR conditions were optimized for the primers and the size of the product expected. 2 µl of cDNA was used in a 20 µl reaction with touchdown cycling conditions. Products were run on an ethidium bromide containing agarose gel, and resulting gel pictures were semi-quantitatively analyzed and scored. The gel pictures of the end-point PCR on the tissue panel were scored on a scale of 1-5. Each picture was scored independently by three people based on visual band intensity and results compiled, scores were compared to confirm all three agreed on the relative intensities of the bands and modifications were made where needed. The median of the three scores was then recorded as the final score.

## II. Results

[0330]

TABLE 4

| Breast Screening Endpoint PCR Data |           |                       |                       |             |            |               |              |
|------------------------------------|-----------|-----------------------|-----------------------|-------------|------------|---------------|--------------|
| Marker                             | Gene Name | Endpoint PCR Primer 1 | Endpoint PCR Primer 2 | Normal Pool | Tumor Pool | Breast Normal | Breast Tumor |
| M196A                              | BCMP11    | 1-20                  | 243-262               | 3           | 3          | 3             | 5            |
| M725                               | BCMP11    | 2-21                  | 523-543               | 0           | 0          | 0             | 2            |
| M726                               | BCMP11    | 1-20                  | 107-126               | 3           | 3          | 3             | 5            |
| M727                               | BCMP11    | 1-20                  | 244-263               | 3           | 3          | 3             | 5            |
| M156                               | CXCL9     | 12-38                 | 479-498               | 0           | 3          | 0             | 4            |
| M419                               | CXCL10    | 29-51                 | 366-385               | 1           | 1          | 2             | 4            |
| M728                               | DNAJC1    | 388-410               | 1155-1179             | 0           | 0          | 0             | 2            |
| M729                               | DNAJC1    | 388-410               | 1137-1161             | 0           | 0          | 0             | 2            |
| M111                               | DNAJC1    | 252-274               | 1775-1799             | 1           | 1          | 2             | 3            |
| M428A                              | FLJ22774  | 528-553               | 3028-3050             |             |            | 0             | 2            |
| M149A                              | LIV-1     | 266-283               | 2612-2638             | 0           | 3          | 2             | 5            |
| M730                               | LIV-1     | 309-324               | 1748-1719             |             |            | 2             | 3            |
| M158A                              | MMP11     | 433-450               | 1518-1536             | 0           | 0          | 0             | 3            |
| M165A                              | NPY1R     | 195-215               | 1440-1459             | 2           | 2          | 3             | 5            |
| M731                               | NPY1R     | 164-184               | 1506-1525             | 2           | 2          | 3             | 5            |
| M732                               | NPY1R     | 195-215               | 1154-1173             | 2           | 2          | 3             | 5            |
| M235                               | NY-BR-1   | 3539-3560             | 4171-4195             | 1           | 0          | 3             | 4            |
| M562                               | PIP       | 4-22                  | 494-509               | 0           | 3          | 4             | 5            |
| M96A                               | SCUBE2    | 342-365               | 3272-3294             | 0           | 0          | 3             | 5            |
| M739                               | SCUBE2    | 342-365               | 3032-3054             | 0           | 0          | 3             | 5            |
| M740                               | SCUBE2    | 342-365               | 2894-2916             | 0           | 0          | 3             | 5            |
| M741                               | SCUBE2    | 342-365               | 3359-3381             | 0           | 0          | 3             | 5            |
| M242                               | TFF1      | 22-42                 | 351-371               | 0           | 0          | 2             | 5            |

[0331] Markers were expressed at higher levels in the breast tumor samples than those obtained from the other tumor samples or the normal sample groups (Table 4). Particular strong expression was observed with M725, M728, M729, M158A, M242, M156, M419, and M149A in the breast tumor group when compared to those obtained from the breast normal, other normal, or the other tumor group.

TABLE 5

| Breast Staging Endpoint PCR Data |                     |                       |                       |              |              |
|----------------------------------|---------------------|-----------------------|-----------------------|--------------|--------------|
| Marker                           | Gene Symbol         | Endpoint PCR Primer 1 | Endpoint PCR Primer 2 | Tum Out Good | Tum Out Poor |
| M672A                            | ASS                 | 69-88                 | 1323-1344             | 1            | 5            |
| M675A                            | CAB2                | 1-21                  | 1153-1177             | 0            | 3            |
| M367                             | CD24                | 6-29                  | 361-384               | 3            | 4            |
| M514                             | DARPP-32, variant 1 | 179-198               | 1201-1220             | 1            | 5            |
| M708                             | DARPP-32, variant 2 | 137-156               | 1541-1560             | 1            | 4            |
| M709                             | FACL2               | 1-24                  | 2307-2332             | 0            | 3            |
| M710                             |                     |                       |                       |              |              |
| M495                             | GSTP1               | 3-22                  | 676-697               | 1            | 3            |
| M674                             | HN1                 | 54-72                 | 601-622               | 2            | 5            |
| M234A                            | MGC14832            | 2-19                  | 374-396               | 2            | 5            |
| M408                             | NDRG1               | 66-85                 | 1374-1393             | 1            | 3            |
| M711                             | ORMDL3              | 287-308               | 874-896               | 0            | 4            |
| M678A                            | PSMB9               | 1-18                  | 739-761               | 1            | 3            |
| M421A                            | SERHL               | 51-69                 | 1103-1122             | 3            | 5            |
| M185A                            | SLPI                | 13-33                 | 519-538               | N/A          | 4            |

[0332] The markers were expressed at higher levels in the breast tumor samples of the poor outcome group than those obtained from the good outcome group (Table 5). Particular strong expression was observed with M672A, M675A, M514, M708, M710, M674, M234A, M711, and M421A in the poor outcome group when compared to those obtained from the good outcome group.

## EXAMPLE 3

## Characterization of OSF-2 Splice Variants

## I. Materials and Methods

**[0333]** cDNA Synthesis

**[0334]** Total RNA was isolated from 3 normal and 12 tumor breast tissue samples similar to procedures described above in Examples 1 and 2. Briefly, using the TRIZOL Reagent (Invitrogen, San Diego, Calif.) System according to manufacturer instructions, followed by RNeasy (Qiagen, Valencia, Calif.) or DNase I (Ambion) treatment according to manufacturers instructions. 1 µg from each sample was combined into normal and tumor pools. ThermoScript RT-PCR System (Invitrogen, San Diego, Calif.) was used to obtain cDNA as described in Example 2 above. The final product was diluted with water to a final volume of 400-800 µl.

**[0335]** cDNA was amplified using OSF-2 gene specific primers from exon 16 and exon 23 to cover the region involved in splice variation. Primers for PCR amplification were designed using Primer Version 5.0 software (Whitehead Institute, Cambridge, Mass.). PCR conditions were optimized for the primers and product size expected. 0.5 µl of diluted RT reaction was used in a 30 µl reaction with PCR conditions, after an initial 95° C. denaturing step of 2 minutes, consisting of 55 cycles of 95° C. for 30 sec, annealing @ 60° C. for 35 sec and elongation temp of 72° C. for 30 sec and a final elongation step of 72° C. for 7 min

## Cloning Colony PCR and Sequencing

**[0336]** PCR products for both reactions derived from RT/PCR were gel-purified and cloned into pCR2.1 using TOPO TA cloning kit and transforming into *E. coli* One-Shot Chemically Competent cells (Invitrogen, San Diego, Calif.) according to manufacturer's instructions. Resulting colonies were selected and colony PCR was carried out in 30 µL volume as described under above using colony cells originating from the normal and the tumor pools as template. Resulting PCR product was purified using QIAquick 96 multiwell kit (Qiagen Inc., Valencia Calif.), and submitted for sequencing. Sequencing was preformed using ABI 3700 Automated Sequencer with Big Dye Terminators version 1.1.

**[0337]** The program BLAST [Kent, 2002] was used to align all clone sequences to genomic sequence of the OSF-2 locus. Only sequences matching the entire variable region of OSF-2, i.e., spanning at least from exon 17 to exon 22 or from exon 21 to exon 16 ("qualifying sequences"), were considered. Sequences were then grouped according to their presence-absence pattern of the variable exons 17-21.

## II. Results

**[0338]** OSF-2 expression is subject to alternative splicing events creating eight transcript variants, which are characterized by different combinations of exons 17 to 21 (of 23 total exons) (see Table 6). Variable exons 17-19 and 21 are positioned within the coding sequence and can be present or absent without changing the transcripts' reading frame, giving rise to different protein products in a modular fashion.

TABLE 6

| Schematic Representation of OSF-2 Alternative Splice Variants |      |      |      |      |      |      |      |
|---------------------------------------------------------------|------|------|------|------|------|------|------|
| Marker ID                                                     | Exon | Exon | Exon | Exon | Exon | Exon | Exon |
| M56A                                                          | 16   | 17   | 18   | 19   | 20   | 21   | 22   |
| M733                                                          | 16   | 17   | 18   | 19   | 20   |      | 22   |
| M734                                                          | 16   |      | 18   | 19   | 20   | 21   | 22   |
| M735                                                          | 16   |      | 18   | 19   | 20   |      | 22   |
| M491A                                                         | 16   |      |      | 19   | 20   | 21   | 22   |
| M736                                                          | 16   |      |      | 19   | 20   |      | 22   |
| M737                                                          | 16   |      |      |      | 20   | 21   | 22   |
| M738                                                          | 16   |      |      |      | 20   |      | 22   |

**[0339]** The relative expression levels of the eight listed splice variants of OSF-2 are different between normal and tumor tissue. Table 7 depicts the relative frequencies of each transcript in normal, and breast tumor tissue as obtained by analyzing qualifying sequences of clones derived from normal breast tissue and breast tumor tissue.

TABLE 7

| Relative frequencies of OSF-2 splice variant transcripts in tissue |                           |                                |                               |
|--------------------------------------------------------------------|---------------------------|--------------------------------|-------------------------------|
| Marker ID                                                          | Description of transcript | % of all transcripts in normal | % of all transcripts in tumor |
| M56A                                                               | (1) all exons, +21        | 10.09                          | 3.50                          |
| M733                                                               | (2) all exons, no 21      | 4.28                           | 2.33                          |
| M734                                                               | (3) no 17, +21            | 31.50                          | 23.03                         |
| M735                                                               | (4) no 17, no 21          | 24.46                          | 32.07                         |
| M491A                                                              | (5) no (17, 18), +21      | 11.62                          | 11.95                         |
| M736                                                               | (6) no (17, 18), no 21    | 12.54                          | 19.83                         |
| M737                                                               | (7) no (17-19), +21       | 0.61                           | 2.33                          |
| M738                                                               | (8) no (17-19), no 21     | 2.45                           | 4.67                          |
|                                                                    | Other transcripts         | 2.45                           | 0.29                          |
| ALL                                                                |                           | 100                            | 100                           |

**[0340]** There is an increased level exon 21 containing transcripts in normal breast tissue, and increased level of transcripts lacking exon 21 in breast tumor tissue, (e.g., a total of 59% of all transcripts in breast tumor tissue lacking exon 21, compared to only 45% of all transcripts lacking exon 21 in normal breast tissue in samples analyzed).

**[0341]** Expression levels were determined for transcripts either containing or lacking exon 21 for OSF-2. Two reagent sets were used: one specific for transcripts containing exon 21 and a second one specific for transcripts that do not. A significant tumor/normal increased expression was observed. For example, an average 2.5-fold over-expression in tumor samples, is observed with the reagent set specific for OSF-2 transcripts lacking exon 21. This increase is not observed in assessing the OSF-2 transcripts containing exon 21. These results reflect both the differences in relative transcript frequencies between normal and tumor tissue as described above and a general overexpression of OSF-2 in tumor tissue as originally observed with transcriptional profiling microarray experiments using probes unable to distinguish between the OSF-2 variants described.

**[0342]** The references cited herein, including journal articles, patents, published patent applications, and database records including GenBank, IMAGE consortium and Derwent cited throughout this application, are hereby incorporated by reference.

## Other Embodiments

[0343] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many

equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

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His Ser Ala Leu Gly Leu Cys Leu Leu Leu Val Thr Val Ser Ser Asn
   5                               10               15

ctt gcc att gca ata aaa aag gaa aag agg cct cct cag aca ctc tca      152
Leu Ala Ile Ala Ile Lys Lys Glu Lys Arg Pro Pro Gln Thr Leu Ser
  20                25               30               35

aga gga tgg gga gat gac atc act tgg gta caa act tat gaa gaa ggt      200
Arg Gly Trp Gly Asp Ile Thr Trp Val Gln Thr Tyr Glu Glu Gly
   40                45               50

ctc ttt tat gct caa aaa agt aag aag cca tta atg gtt att cat cac      248
Leu Phe Tyr Ala Gln Lys Ser Lys Lys Pro Leu Met Val Ile His His
   55                60               65

ctg gag gat tgt caa tac tct caa gca cta aag aaa gta ttt gcc caa      296
Leu Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val Phe Ala Gln
   70                75               80

aat gaa gaa ata caa gaa atg gct cag aat aag ttc atc atg cta aac      344
Asn Glu Glu Ile Gln Glu Met Ala Gln Asn Lys Phe Ile Met Leu Asn
   85                90               95

ctt atg cat gaa acc act gat aag aat tta tca cct gat ggg caa tat      392
Leu Met His Glu Thr Thr Asp Lys Asn Leu Ser Pro Asp Gly Gln Tyr
  100                105              110              115

gtg cct aga atc atg ttt gta gac cct tct tta aca gtt aga gct gac      440
Val Pro Arg Ile Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp
  120                125              130

ata gct gga aga tac tct aac aga ttg tac aca tat gag cct cgg gat      488
Ile Ala Gly Arg Tyr Ser Asn Arg Leu Tyr Thr Tyr Glu Pro Arg Asp
  135                140              145

tta ccc cta ttg ata gaa aac atg aag aaa gca tta aga ctt att cag      536
Leu Pro Leu Leu Ile Glu Asn Met Lys Lys Ala Leu Arg Leu Ile Gln
  150                155              160

tca gag cta taa gagatgatag aaaaaagcct tcacttcaaa gaagtcaaat      588
Ser Glu Leu *
  165

ttcatgaaga aaacctctgg cacattgaca aatac      623

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20          25          30

Thr Leu Ser Arg Gly Trp Gly Asp Asp Ile Thr Trp Val Gln Thr Tyr
35          40          45

Glu Glu Gly Leu Phe Tyr Ala Gln Lys Ser Lys Lys Pro Leu Met Val
50          55          60

Ile His His Leu Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val
65          70          75          80

Phe Ala Gln Asn Glu Glu Ile Gln Glu Met Ala Gln Asn Lys Phe Ile
85          90          95

Met Leu Asn Leu Met His Glu Thr Thr Asp Lys Asn Leu Ser Pro Asp
100         105         110

Gly Gln Tyr Val Pro Arg Ile Met Phe Val Asp Pro Ser Leu Thr Val
115        120        125

Arg Ala Asp Ile Ala Gly Arg Tyr Ser Asn Arg Leu Tyr Thr Tyr Glu
130        135        140

Pro Arg Asp Leu Pro Leu Leu Ile Glu Asn Met Lys Lys Ala Leu Arg
145        150        155        160

Leu Ile Gln Ser Glu Leu
165

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                                   Met Met Leu
                                   1

cac tca gct ttg ggt ctc tgc ctc tta ctc gtc aca gtt tct tcc aac      105
His Ser Ala Leu Gly Leu Cys Leu Leu Leu Val Thr Val Ser Ser Asn
5          10          15

ctt gcc att gca ata aaa aag gaa aag agg cct cct cag aca ctc tca      153
Leu Ala Ile Ala Ile Lys Lys Glu Lys Arg Pro Pro Gln Thr Leu Ser
20          25          30          35

aga gga tgg gga gat gac atc act tgg gta caa act tat gaa gaa ggt      201
Arg Gly Trp Gly Asp Asp Ile Thr Trp Val Gln Thr Tyr Glu Glu Gly
40          45          50

ctc ttt tat gct caa aaa agt aag aag cca tta atg gtt att cat cac      249
Leu Phe Tyr Ala Gln Lys Ser Lys Lys Pro Leu Met Val Ile His His
55          60          65

ctg gag gat tgt caa tac tct caa gca cta aag aaa gta ttt gcc caa      297
Leu Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val Phe Ala Gln
70          75          80

aat gaa gaa ata caa gaa atg gct cag aat aag ttc atc atg cta aac      345
Asn Glu Glu Ile Gln Glu Met Ala Gln Asn Lys Phe Ile Met Leu Asn
85          90          95

ctt atg cat gaa acc act gat aag aat tta tca cct gat ggg caa tat      393
Leu Met His Glu Thr Thr Asp Lys Asn Leu Ser Pro Asp Gly Gln Tyr

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-continued

| 100                                                             | 105 | 110 | 115 |     |
|-----------------------------------------------------------------|-----|-----|-----|-----|
| gtg cct aga atc atg ttt gta gac cct tct tta aca gtt aga gct gac |     |     |     | 441 |
| Val Pro Arg Ile Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp |     |     |     |     |
|                                                                 | 120 | 125 | 130 |     |
| ata gct gga aga tac tct aac aga ttg tac aca tat gag cct cgg gat |     |     |     | 489 |
| Ile Ala Gly Arg Tyr Ser Asn Arg Leu Tyr Thr Tyr Glu Pro Arg Asp |     |     |     |     |
|                                                                 | 135 | 140 | 145 |     |
| tta ccc cta taa gaaatttgga tacagagaca tgcatacaga aggaatgccca    |     |     |     | 541 |
| Leu Pro Leu *                                                   |     |     |     |     |
|                                                                 | 150 |     |     |     |
| tg                                                              |     |     |     | 543 |

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 <212> TYPE: PRT  
 <213> ORGANISM: human

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| 1 5 10 15                                                       |  |
| Ser Ser Asn Leu Ala Ile Ala Ile Lys Lys Glu Lys Arg Pro Pro Gln |  |
| 20 25 30                                                        |  |
| Thr Leu Ser Arg Gly Trp Gly Asp Asp Ile Thr Trp Val Gln Thr Tyr |  |
| 35 40 45                                                        |  |
| Glu Glu Gly Leu Phe Tyr Ala Gln Lys Ser Lys Lys Pro Leu Met Val |  |
| 50 55 60                                                        |  |
| Ile His His Leu Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val |  |
| 65 70 75 80                                                     |  |
| Phe Ala Gln Asn Glu Glu Ile Gln Glu Met Ala Gln Asn Lys Phe Ile |  |
| 85 90 95                                                        |  |
| Met Leu Asn Leu Met His Glu Thr Thr Asp Lys Asn Leu Ser Pro Asp |  |
| 100 105 110                                                     |  |
| Gly Gln Tyr Val Pro Arg Ile Met Phe Val Asp Pro Ser Leu Thr Val |  |
| 115 120 125                                                     |  |
| Arg Ala Asp Ile Ala Gly Arg Tyr Ser Asn Arg Leu Tyr Thr Tyr Glu |  |
| 130 135 140                                                     |  |
| Pro Arg Asp Leu Pro Leu                                         |  |
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| agggtctcttt tatgtctaaa aaagtaagaa gccatta atg gtt att cat cac ctg  | 115                     |
|                                                                    | Met Val Ile His His Leu |
|                                                                    | 1 5                     |
| gag gat tgt caa tac tct caa gca cta aag aaa gta ttt gcc caa aat    | 163                     |
| Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val Phe Ala Gln Asn    |                         |
|                                                                    | 10 15 20                |
| gaa gaa ata caa gaa atg gct cag aat aag ttc atc atg cta aac ctt    | 211                     |

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| aagagcactg | gccaa | gtcag | gcttcttctg | agagagtctc | tagaagac | atg | atg | cta | 57  |     |     |     |     |     |     |     |
|            |       |       |            |            |          | Met | Met | Leu |     |     |     |     |     |     |     |     |
|            |       |       |            |            |          | 1   |     |     |     |     |     |     |     |     |     |     |
| cac        | tca   | gct   | ttg        | ggc        | ctc      | tgc | ctc | tta | ctc | gtc | aca | gtt | tct | tcc | aac | 105 |
| His        | Ser   | Ala   | Leu        | Gly        | Leu      | Cys | Leu | Leu | Leu | Val | Thr | Val | Ser | Ser | Asn |     |
|            | 5     |       |            |            |          | 10  |     |     |     |     | 15  |     |     |     |     |     |
| ctt        | gcc   | att   | qca        | ata        | aaa      | aaq | qaa | aaq | aqg | cct | cct | caq | aca | ctc | tca | 153 |

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Leu Ala Ile Ala Ile Lys Lys Glu Lys Arg Pro Pro Gln Thr Leu Ser
20          25          30          35

aga gga tgg gga gat gac atc act tgg gta caa act tat gaa gaa ggt    201
Arg Gly Trp Gly Asp Asp Ile Thr Trp Val Gln Thr Tyr Glu Glu Gly
          40          45          50

ctc ttt tat gct caa aaa agt aag aag cca tta atg gtt att cat cac    249
Leu Phe Tyr Ala Gln Lys Ser Lys Lys Pro Leu Met Val Ile His His
          55          60          65

ctg gag gat tgt caa tac tct caa gca cta aag aaa gta ttt gcc caa    297
Leu Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val Phe Ala Gln
          70          75          80

aat gaa gaa ata caa gaa atg gct cag aat aag ttc atc atg cta aac    345
Asn Glu Glu Ile Gln Glu Met Ala Gln Asn Lys Phe Ile Met Leu Asn
          85          90          95

ctt atg cat gaa acc act gat aag aat tta tca cct gat ggg caa tat    393
Leu Met His Glu Thr Thr Asp Lys Asn Leu Ser Pro Asp Gly Gln Tyr
          100          105          110          115

gtg cct aga atc atg ttt gta gtg ata gaa aac atg aag aaa gca tta    441
Val Pro Arg Ile Met Phe Val Val Ile Glu Asn Met Lys Lys Ala Leu
          120          125          130

aga ctt att cag tca gag cta taa gagatgatgg aaaaaagcct tcacttcaaa    495
Arg Leu Ile Gln Ser Glu Leu *
          135

gaagtcaaat ttcataaga aaacctctgg cacattgaca aatactaaat gtgcaagtat    555

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taaatgtttt ttaaa    630

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          20          25          30

Thr Leu Ser Arg Gly Trp Gly Asp Asp Ile Thr Trp Val Gln Thr Tyr
          35          40          45

Glu Glu Gly Leu Phe Tyr Ala Gln Lys Ser Lys Lys Pro Leu Met Val
          50          55          60

Ile His His Leu Glu Asp Cys Gln Tyr Ser Gln Ala Leu Lys Lys Val
          65          70          75          80

Phe Ala Gln Asn Glu Glu Ile Gln Glu Met Ala Gln Asn Lys Phe Ile
          85          90          95

Met Leu Asn Leu Met His Glu Thr Thr Asp Lys Asn Leu Ser Pro Asp
          100          105          110

Gly Gln Tyr Val Pro Arg Ile Met Phe Val Val Ile Glu Asn Met Lys
          115          120          125

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                               1       5

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Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val Leu Ile Gly Val Gln
                               10       15       20

gga acc cca gta gtg aga aag ggt cgc tgt tcc tgc atc agc acc aac      150
Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser Cys Ile Ser Thr Asn
                               25       30       35

caa ggg act atc cac cta caa tcc ttg aaa gac ctt aaa caa ttt gcc      198
Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp Leu Lys Gln Phe Ala
                               40       45       50

cca agc cct tcc tgc gag aaa att gaa atc att gct aca ctg aag aat      246
Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile Ala Thr Leu Lys Asn
                               55       60       65

gga gtt caa aca tgt cta aac cca gat tca gca gat gtg aag gaa ctg      294
Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala Asp Val Lys Glu Leu
                               70       75       80       85

att aaa aag tgg gag aaa cag gtc agc caa aag aaa aag caa aag aat      342
Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys Lys Lys Gln Lys Asn
                               90       95       100

ggg aaa aaa cat caa aaa aag aaa gtt ctg aaa gtt cga aaa tct caa      390
Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys Val Arg Lys Ser Gln
                               105       110       115

cgt tct cgt caa aag aag act aca taa gagaccactt caccaataag      437
Arg Ser Arg Gln Lys Lys Thr *
                               120       125

tattctgtgt taaaaatgtt ctattttaat tataccgcta tcattccaaa ggaggatggc      497

atataataca aaggcttatt aatttgacta gaaaatttaa aacattactc tgaattgta      557

actaaagtta gaaagttgat tttaagaatc caaacgttaa gaattgttaa aggctatgat      617

tgtctttgtt cttctaccac ccaccagttg aatttcatca tgcttaaggc catgatttta      677

gcaataccca tgtctacaca gatgttcacc caaccacatc ccaactcaca cagctgcctg      737

gaagagcagc cctaggcttc cacgtactgc agcctccaga gagtatctga ggcacatgtc      797

agcaagtcct aagcctgtta gcatgctggt gagccaagca gtttgaaatt gagctggacc      857

tcaccaagct gctgtggcca tcaacctctg tatttgaatc agcctacagg cctcacacac      917

aatgtgtctg agagattcat gctgattgtt attgggtatc accactggag atcaccagtg      977

tgtggctttc agagcctcct ttctggcttt ggaagccatg tgattccatc ttgcccgttc      1037

aggetgacca ctttattttc ttttgttccc ctttgettca ttcaagtcag ctcttttcca      1097

tcctaccaca atgcagtgcc tttcttctct ccagtgcacc tgtcatatgc tctgatttat      1157

ctgagtcaac tcctttctca tcttgtcccc aacaccccac agaagtgtt tcttctccca      1217

atcctcctc actcagtcga gcttagttca agtctctgct cttaaataaa cctttttgga      1277

cacacaaatt atcttaaaac tcctgtttca cttgggttcag taccacatgg gtgaacactc      1337

aatgggtaac taattcttgg gtgtttatcc tatctctcca accagattgt cagctccttg      1397

agggcaagag ccacagtata tttccctggt tcttccacag tgcctaataa tactgtggaa      1457

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ctagggttta ataatttttt aattgatgtt gttatgggca ggatggcaac cagaccattg 1517
tctcagagca ggtgctggct ctttcctggc tactccatgt tggctagcct ctggtaacct 1577
cttacttatt atcttcagga cactcactac agggaccagg gatgatgcaa catccttgtc 1637
tttttatgac aggatgtttg ctcagcttct ccaacaataa gaagcacgtg gtaaaacact 1697
tgcggatatt ctggactgtt tttaaaaaat atacagttta cggaaaatca tataatctta 1757
caatgaaaag gactttatag atcagccagt gaccaacctt tccccacca taaaaaatt 1817
ccttttcccc aaggaaaagg gctttctcaa taagcctcag ctttctaaga tctaacaaga 1877
tagccaccga gatccttate gaaactcatt ttaggcaaat atgagtttta ttgtccgttt 1937
acttgtttca gagtgtgtat tgtgattatc aattaccaca ccatctccca tgaagaaagg 1997
gaacggtgaa gtactaagcg cttagaggaag cagccaagtc ggttagtgga agcatgattg 2057
gtgccagtt agcctctgca ggatgtggaa acctccttcc aggggagggt cagtgaattg 2117
tgtaggagag gttgtctgtg gccagaattt aaacctatac tcactttccc aaattgaatc 2177
actgctcaca ctgctgatga tttagagtgc tgtccggtgg agatcccacc cgaacgtctt 2237
atctaateat gaaactcctt agttccttca tgtaacttcc ctgaaaaatc taagtgtttc 2297
ataaatttga gagtctgtga cccacttacc ttgcatctca caggtagaca gtatataact 2357
aacaacaaaa gactacatat tgtcactgac acacacgtta taatcattta tcatatatat 2417
acatacatgc atacactctc aaagcaaata atttttcact tcaaacacgt attgacttgt 2477
ataccttgta atttgaaata ttttctttgt taaaatagaa tggatatcaat aaatagacca 2537
ttaatcag 2545

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<210> SEQ ID NO 10
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 10

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Met Lys Lys Ser Gly Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val
1             5             10            15
Leu Ile Gly Val Gln Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser
20            25            30
Cys Ile Ser Thr Asn Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp
35            40            45
Leu Lys Gln Phe Ala Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile
50            55            60
Ala Thr Leu Lys Asn Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala
65            70            75            80
Asp Val Lys Glu Leu Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys
85            90            95
Lys Lys Gln Lys Asn Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys
100           105           110
Val Arg Lys Ser Gln Arg Ser Arg Gln Lys Lys Thr Thr
115           120           125

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<210> SEQ ID NO 11
<211> LENGTH: 1172
<212> TYPE: DNA
<213> ORGANISM: human

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<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (67) ... (363)

<400> SEQUENCE: 11

gagacattcc tcaattgctt agacatatcc tgagcctaca gcagaggaac ctccagtctc      60
agcacc atg aat caa act gcg att ctg att tgc tgc ctt atc ttt ctg      108
      Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu
        1             5             10

act cta agt ggc att caa gga gta cct ctg tct aga acc gta cgc tgt      156
Thr Leu Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys
15             20             25             30

acc tgc atc agc att agt aat caa cct gtt aat cca agg tct tta gaa      204
Thr Cys Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu
             35             40             45

aaa ctt gaa att att cct gca agc caa ttt tgt cca cgt gtt gag atc      252
Lys Leu Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile
             50             55             60

att gct aca atg aaa aag aag ggt gag aag aga tgt ctg aat cca gaa      300
Ile Ala Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu
        65             70             75

tcg aag gcc atc aag aat tta ctg aaa gca gtt agc aag gaa atg tct      348
Ser Lys Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser
        80             85             90

aaa aga tct cct taa aaccagaggg gagcaaaatc gatgcagtgc ttccaaggat      403
Lys Arg Ser Pro *
95

ggaccacaca gaggtgcct ctcccatcac ttccctacat ggagtatatg tcaagccata      463
attgtttctta gtttgcagtt acactaaaag gtgaccaatg atggtcacca aatcagctgc      523
tactactcct gtaggaaggt taatgttcat catcctaagc tattcagtaa taactctacc      583
ctggcactat aatgtaagct ctactgaggt gctatgttct tagtggatgt tctgaccctg      643
cttcaaatat ttccctcacc ttcccatct tccaagggta ctaaggaatc tttctgcttt      703
ggggtttatc agaattctca gaattctaaa taactaaaag gtatgcaatc aaatctgctt      763
tttaaagaat gctctttact tcatggactt ccaactgcat cctcccaagg ggcccaaatt      823
ctttcagtgg ctacctacat acaattccaa acacatacag gaaggtagaa atatctgaaa      883
atgtatgtgt aagtattctt atttaatgaa agactgtaca aagtataagt cttagatgta      943
tatatttctt atattgtttt cagtgtacat ggaataacat gtaattaagt actatgtatc     1003
aatgagtaac aggaaaaattt taaaaataca gatagatata tgctctgcat gttacataag     1063
ataaatgtgc tgaatggttt tcaaataaaa atgaggtact ctctggaaa tattaagaaa     1123
gactatctaa atgttgaaag atcaaaaggt taataaagta attataact                     1172

<210> SEQ ID NO 12
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 12

Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
1             5             10             15

Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
20             25             30

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|                                                                 |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|-----------------------------------------------------------------|------------|------------|------------|------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Ile                                                             | Ser        | Ile        | Ser        | Asn        | Gln         | Pro | Val | Asn | Pro | Arg | Ser | Leu | Glu | Lys | Leu |  |
|                                                                 | 35         |            |            |            |             |     | 40  |     |     |     |     | 45  |     |     |     |  |
| Glu                                                             | Ile        | Ile        | Pro        | Ala        | Ser         | Gln | Phe | Cys | Pro | Arg | Val | Glu | Ile | Ile | Ala |  |
|                                                                 | 50         |            |            |            |             | 55  |     |     |     | 60  |     |     |     |     |     |  |
| Thr                                                             | Met        | Lys        | Lys        | Lys        | Gly         | Glu | Lys | Arg | Cys | Leu | Asn | Pro | Glu | Ser | Lys |  |
| 65                                                              |            |            |            |            | 70          |     |     |     | 75  |     |     |     |     |     | 80  |  |
| Ala                                                             | Ile        | Lys        | Asn        | Leu        | Leu         | Lys | Ala | Val | Ser | Lys | Glu | Met | Ser | Lys | Arg |  |
|                                                                 |            |            | 85         |            |             |     |     |     | 90  |     |     |     |     | 95  |     |  |
| Ser                                                             | Pro        |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <br><210> SEQ ID NO 13                                          |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <211> LENGTH: 1261                                              |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <212> TYPE: DNA                                                 |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <213> ORGANISM: human                                           |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <220> FEATURE:                                                  |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <221> NAME/KEY: CDS                                             |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <222> LOCATION: (244) ... (1152)                                |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| <br><400> SEQUENCE: 13                                          |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| ggcgagggtc                                                      | ttcggaacgt | agcgctggct | gcggccccgc | ccgcctaccc | acccgcccgt  |     | 60  |     |     |     |     |     |     |     |     |  |
| ccggcagccg                                                      | gtccccgcg  | cctccgcgct | ctgtctgggg | ccagccacct | ggcgggcccgc |     | 120 |     |     |     |     |     |     |     |     |  |
| tccgggtgcgc                                                     | ctgcccgcgc | ttttactga  | caggcgctgt | tccccacagc | cagcgccgcc  |     | 180 |     |     |     |     |     |     |     |     |  |
| cgccacgtcc                                                      | cagctctcgg | ccaacggagc | tgcgcgccgg | gtgacctttc | cgagcccagc  |     | 240 |     |     |     |     |     |     |     |     |  |
| gcg atg acg gct cct tgc tcc cag ccg gcg cag ctt cct gga cgc cgc |            |            |            |            |             |     | 288 |     |     |     |     |     |     |     |     |  |
| Met Thr Ala Pro Cys Ser Gln Pro Ala Gln Leu Pro Gly Arg Arg     |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| 1 5 10 15                                                       |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
| cag ctc ggg ctg gtg ccg ttc ccg ccg ccg ccg ccg ccg acg ccg ctg |            |            |            |            |             |     | 336 |     |     |     |     |     |     |     |     |  |
| Gln Leu Gly Leu Val Pro Phe Pro Pro Pro Pro Arg Thr Pro Leu     |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 20         |            |            |            |             | 25  |     |     |     |     | 30  |     |     |     |     |  |
| ctg tgg ctg ctg ctg ctg ctg gcc gcc gtg gcg ccg gcg cgc ggc     |            |            |            |            |             |     | 384 |     |     |     |     |     |     |     |     |  |
| Leu Trp Leu Leu Leu Leu Leu Ala Ala Val Ala Pro Ala Arg Gly     |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 35         |            |            |            |             | 40  |     |     |     | 45  |     |     |     |     |     |  |
| tgg gag agc gga gac ctg gag ttg ttt gac tta gtg gag gag gtg cag |            |            |            |            |             |     | 432 |     |     |     |     |     |     |     |     |  |
| Trp Glu Ser Gly Asp Leu Glu Leu Phe Asp Leu Val Glu Glu Val Gln |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 50         |            |            |            | 55          |     |     |     | 60  |     |     |     |     |     |     |  |
| ctc aac ttc tac cag ttc ctc ggg gtg cag cag gca cct gaa tgg aca |            |            |            |            |             |     | 480 |     |     |     |     |     |     |     |     |  |
| Leu Asn Phe Tyr Gln Phe Leu Gly Val Gln Gln Ala Pro Glu Trp Thr |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 65         |            |            |            | 70          |     |     |     | 75  |     |     |     |     |     |     |  |
| gaa gag gac ctc agc caa ctg aca aga agt atg gtt aag ttc cca gga |            |            |            |            |             |     | 528 |     |     |     |     |     |     |     |     |  |
| Glu Glu Asp Leu Ser Gln Leu Thr Arg Ser Met Val Lys Phe Pro Gly |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 80         |            |            |            | 85          |     |     |     | 90  |     |     |     |     | 95  |     |  |
| ggg act cca ggt cga tgg gaa aag att gcc cac gaa ttg ggt cga tct |            |            |            |            |             |     | 576 |     |     |     |     |     |     |     |     |  |
| Gly Thr Pro Gly Arg Trp Glu Lys Ile Ala His Glu Leu Gly Arg Ser |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 100        |            |            |            |             | 105 |     |     |     |     | 110 |     |     |     |     |  |
| gtg aca gat gtg aca acc aaa gcc aag caa ctg aag gat tca gtg acc |            |            |            |            |             |     | 624 |     |     |     |     |     |     |     |     |  |
| Val Thr Asp Val Thr Thr Lys Ala Lys Gln Leu Lys Asp Ser Val Thr |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 115        |            |            |            |             | 120 |     |     |     |     | 125 |     |     |     |     |  |
| tgc tcc cca gga atg gtt aga ctc tcc gaa ctc aaa tcg aca gtt cag |            |            |            |            |             |     | 672 |     |     |     |     |     |     |     |     |  |
| Cys Ser Pro Gly Met Val Arg Leu Ser Glu Leu Lys Ser Thr Val Gln |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 130        |            |            |            |             | 135 |     |     |     |     | 140 |     |     |     |     |  |
| aat tcc agg ccc atc aaa acg gcc acc acc ttg ccc gat gac atg atc |            |            |            |            |             |     | 720 |     |     |     |     |     |     |     |     |  |
| Asn Ser Arg Pro Ile Lys Thr Ala Thr Thr Leu Pro Asp Asp Met Ile |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 145        |            |            |            | 150         |     |     |     |     |     | 155 |     |     |     |     |  |
| acc cag cga gag gac gca gag ggg gtg gca gcg gag gag gag cag gag |            |            |            |            |             |     | 768 |     |     |     |     |     |     |     |     |  |
| Thr Gln Arg Glu Asp Ala Glu Gly Val Ala Ala Glu Glu Glu Gln Glu |            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |  |
|                                                                 | 160        |            |            |            | 165         |     |     |     | 170 |     |     |     |     | 175 |     |  |

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|                                                                   |      |
|-------------------------------------------------------------------|------|
| gga gac tcc ggt gag cag gag acc ggg gcc act gat gcc cgg cct cgg   | 816  |
| Gly Asp Ser Gly Gln Glu Thr Gly Ala Thr Asp Ala Arg Pro Arg       |      |
| 180 185 190                                                       |      |
| agg cgg aag cca gcc agg ctg ctg gag gct aca gcg aag ccg gag cca   | 864  |
| Arg Arg Lys Pro Ala Arg Leu Leu Glu Ala Thr Ala Lys Pro Glu Pro   |      |
| 195 200 205                                                       |      |
| gag gag aag tcc aga gcc aag cgg cag aag gac ttt gac ata gca gaa   | 912  |
| Glu Glu Lys Ser Arg Ala Lys Arg Gln Lys Asp Phe Asp Ile Ala Glu   |      |
| 210 215 220                                                       |      |
| caa aac gag tcc agc gac gag gag agc ctg aga aaa gag aga gct cgg   | 960  |
| Gln Asn Glu Ser Ser Asp Glu Glu Ser Leu Arg Lys Glu Arg Ala Arg   |      |
| 225 230 235                                                       |      |
| tct gca gag gag ccg tgg act caa aat caa cag aaa ctt ctg gaa ctg   | 1008 |
| Ser Ala Glu Glu Pro Trp Thr Gln Asn Gln Gln Lys Leu Leu Glu Leu   |      |
| 240 245 250 255                                                   |      |
| gcg ttg cag cag tac cca agg gga tcc tct gac cgc tgg gac aaa ata   | 1056 |
| Ala Leu Gln Gln Tyr Pro Arg Gly Ser Ser Asp Arg Trp Asp Lys Ile   |      |
| 260 265 270                                                       |      |
| gcc aga tgt gtc ccg tcc aag agc aag gaa gac tgt atc gct agg tac   | 1104 |
| Ala Arg Cys Val Pro Ser Lys Ser Lys Glu Asp Cys Ile Ala Arg Tyr   |      |
| 275 280 285                                                       |      |
| aag ttg ctg gtt gaa ctg gtc caa aag aaa aaa caa gct aaa agc tga   | 1152 |
| Lys Leu Leu Val Glu Leu Val Gln Lys Lys Lys Gln Ala Lys Ser *     |      |
| 290 295 300                                                       |      |
| atattctggg agatgatgtt caccttcatt ttccaaaatg aatatcttaa aaatcttatg | 1212 |
| cagaaatttg cattttgtac ctcaatatatt ctacgtcatg tgccttagt            | 1261 |

<210> SEQ ID NO 14  
 <211> LENGTH: 302  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 14

|                                                                 |  |
|-----------------------------------------------------------------|--|
| Met Thr Ala Pro Cys Ser Gln Pro Ala Gln Leu Pro Gly Arg Arg Gln |  |
| 1 5 10 15                                                       |  |
| Leu Gly Leu Val Pro Phe Pro Pro Pro Pro Pro Arg Thr Pro Leu Leu |  |
| 20 25 30                                                        |  |
| Trp Leu Leu Leu Leu Leu Ala Ala Val Ala Pro Ala Arg Gly Trp     |  |
| 35 40 45                                                        |  |
| Glu Ser Gly Asp Leu Glu Leu Phe Asp Leu Val Glu Glu Val Gln Leu |  |
| 50 55 60                                                        |  |
| Asn Phe Tyr Gln Phe Leu Gly Val Gln Gln Ala Pro Glu Trp Thr Glu |  |
| 65 70 75 80                                                     |  |
| Glu Asp Leu Ser Gln Leu Thr Arg Ser Met Val Lys Phe Pro Gly Gly |  |
| 85 90 95                                                        |  |
| Thr Pro Gly Arg Trp Glu Lys Ile Ala His Glu Leu Gly Arg Ser Val |  |
| 100 105 110                                                     |  |
| Thr Asp Val Thr Thr Lys Ala Lys Gln Leu Lys Asp Ser Val Thr Cys |  |
| 115 120 125                                                     |  |
| Ser Pro Gly Met Val Arg Leu Ser Glu Leu Lys Ser Thr Val Gln Asn |  |
| 130 135 140                                                     |  |
| Ser Arg Pro Ile Lys Thr Ala Thr Thr Leu Pro Asp Asp Met Ile Thr |  |
| 145 150 155 160                                                 |  |
| Gln Arg Glu Asp Ala Glu Gly Val Ala Ala Glu Glu Glu Gln Glu Gly |  |

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| 165 |     |     |     |     |     |     |     |     |     | 170 |     |     |     |     |     |  |  |  |  | 175 |  |  |  |  |  |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|-----|--|--|--|--|--|--|--|--|--|
| Asp | Ser | Gly | Glu | Gln | Glu | Thr | Gly | Ala | Thr | Asp | Ala | Arg | Pro | Arg | Arg |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Arg | Lys | Pro | Ala | Arg | Leu | Leu | Glu | Ala | Thr | Ala | Lys | Pro | Glu | Pro | Glu |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Glu | Lys | Ser | Arg | Ala | Lys | Arg | Gln | Lys | Asp | Phe | Asp | Ile | Ala | Glu | Gln |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Asn | Glu | Ser | Ser | Asp | Glu | Glu | Ser | Leu | Arg | Lys | Glu | Arg | Ala | Arg | Ser |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     | 225 |     |     |     | 230 |     |     |     |     |     | 235 |     |     |     | 240 |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Ala | Glu | Glu | Pro | Trp | Thr | Gln | Asn | Gln | Gln | Lys | Leu | Leu | Glu | Leu | Ala |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     |     | 255 |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Leu | Gln | Gln | Tyr | Pro | Arg | Gly | Ser | Ser | Asp | Arg | Trp | Asp | Lys | Ile | Ala |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     |     | 260 |     |     |     | 265 |     |     |     |     |     | 270 |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Arg | Cys | Val | Pro | Ser | Lys | Ser | Lys | Glu | Asp | Cys | Ile | Ala | Arg | Tyr | Lys |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
| Leu | Leu | Val | Glu | Leu | Val | Gln | Lys | Lys | Lys | Gln | Ala | Lys | Ser |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |  |  |  |     |  |  |  |  |  |  |  |  |  |

<210> SEQ ID NO 15  
 <211> LENGTH: 1243  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (244) ... (1134)

<400> SEQUENCE: 15

|                                                                   |     |
|-------------------------------------------------------------------|-----|
| ggcgagggtc ttcggaacgt agcgctggct gcggccccgc ccgcctaccc acccgcccgt | 60  |
| ccggcagccg gctccccgcg cctccgcgct ctgtctgggg ccagccacct ggcgggccgc | 120 |
| tccggtgcgc ctgcccgcgc ttttactga caggcgctgt tccccacagc cagcgccgcc  | 180 |
| cgccacgtcc cagctctcgg ccaacggagc tgcgcggcgg gtgacctttc cgagcccagc | 240 |
| gcg atg acg gct cct tgc tcc cag ccg gcg cag ctt cct gga cgc cgc   | 288 |
| Met Thr Ala Pro Cys Ser Gln Pro Ala Gln Leu Pro Gly Arg Arg       |     |
| 1 5 10 15                                                         |     |
| cag ctc ggg ctg gtg ccg ttc ccg ccg ccg ccg ccg acg ccg ctg       | 336 |
| Gln Leu Gly Leu Val Pro Phe Pro Pro Pro Arg Thr Pro Leu           |     |
| 20 25 30                                                          |     |
| ctg tgg ctg ctg ctg ctg ctg ctg gcc gcc gtg gcg ccg gcg cgc ggc   | 384 |
| Leu Trp Leu Leu Leu Leu Leu Leu Ala Ala Val Ala Pro Ala Arg Gly   |     |
| 35 40 45                                                          |     |
| tgg gag agc gga gac ctg gag ttg ttt gac tta gtg gag gag gtg cag   | 432 |
| Trp Glu Ser Gly Asp Leu Glu Leu Phe Asp Leu Val Glu Glu Val Gln   |     |
| 50 55 60                                                          |     |
| ctc aac ttc tac cag ttc ctc ggg gtg cag cag gat gca tca tct gca   | 480 |
| Leu Asn Phe Tyr Gln Phe Leu Gly Val Gln Gln Asp Ala Ser Ser Ala   |     |
| 65 70 75                                                          |     |
| gac atc aga aaa gca tat cgt aag ctt tca cta act tta cat cca gac   | 528 |
| Asp Ile Arg Lys Ala Tyr Arg Lys Leu Ser Leu Thr Leu His Pro Asp   |     |
| 80 85 90 95                                                       |     |
| aag aat aaa gat gaa aat gca gaa act cag ttt aga caa gtg aca acc   | 576 |
| Lys Asn Lys Asp Glu Asn Ala Glu Thr Gln Phe Arg Gln Val Thr Thr   |     |
| 100 105 110                                                       |     |
| aaa gcc aag caa ctg aag gat tca gtg acc tgc tcc cca gga atg gtt   | 624 |
| Lys Ala Lys Gln Leu Lys Asp Ser Val Thr Cys Ser Pro Gly Met Val   |     |
| 115 120 125                                                       |     |

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aga ctc tcc gaa ctc aaa tcg aca gtt cag aat tcc agg ccc atc aaa      672
Arg Leu Ser Glu Leu Lys Ser Thr Val Gln Asn Ser Arg Pro Ile Lys
      130                      135                      140

acg gcc acc acc ttg ccc gat gac atg atc acc cag cga gag gac gca      720
Thr Ala Thr Thr Leu Pro Asp Asp Met Ile Thr Gln Arg Glu Asp Ala
      145                      150                      155

gag ggg gtg gca gcg gag gag gag cag gag gga gac tcc ggt gag cag      768
Glu Gly Val Ala Ala Glu Glu Glu Gln Glu Gly Asp Ser Gly Glu Gln
      160                      165                      170                      175

gag acc ggg gcc act gat gcc cgg cct cgg agg cgg aag cca gcc agg      816
Glu Thr Gly Ala Thr Asp Ala Arg Pro Arg Arg Arg Lys Pro Ala Arg
      180                      185                      190

ctg ctg gag gct aca gcg aag ccg gag cca gag gag aag tcc aga gcc      864
Leu Leu Glu Ala Thr Ala Lys Pro Glu Pro Glu Glu Lys Ser Arg Ala
      195                      200                      205

aag cgg cag aag gac ttt gac ata gca gaa caa aac gag tcc agc gac      912
Lys Arg Gln Lys Asp Phe Asp Ile Ala Glu Gln Asn Glu Ser Ser Asp
      210                      215                      220

gag gag agc ctg aga aaa gag aga gct cgg tct gca gag gag ccg tgg      960
Glu Glu Ser Leu Arg Lys Glu Arg Ala Arg Ser Ala Glu Glu Pro Trp
      225                      230                      235

act caa aat caa cag aaa ctt ctg gaa ctg gcg ttg cag cag tac cca      1008
Thr Gln Asn Gln Gln Lys Leu Leu Glu Leu Ala Leu Gln Gln Tyr Pro
      240                      245                      250                      255

agg gga tcc tct gac cgc tgg gac aaa ata gcc aga tgt gtc ccg tcc      1056
Arg Gly Ser Ser Asp Arg Trp Asp Lys Ile Ala Arg Cys Val Pro Ser
      260                      265                      270

aag agc aag gaa gac tgt atc gct agg tac aag ttg ctg gtt gaa ctg      1104
Lys Ser Lys Glu Asp Cys Ile Ala Arg Tyr Lys Leu Leu Val Glu Leu
      275                      280                      285

gtc caa aag aaa aaa caa gct aaa agc tga atattctggg agatgatgtt      1154
Val Gln Lys Lys Lys Gln Ala Lys Ser *
      290                      295

caccttcatt ttccaaatg aatatcttaa aaatcttatg cagaaatttg cattttgtac      1214

ctcaatatatt ctacgtcatg tgccttagt                                     1243

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<210> SEQ ID NO 16
<211> LENGTH: 296
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 16

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

Leu Gly Leu Val Pro Phe Pro Pro Pro Pro Pro Arg Thr Pro Leu Leu
      20          25          30

Trp Leu Leu Leu Leu Leu Leu Ala Ala Val Ala Pro Ala Arg Gly Trp
      35          40          45

Glu Ser Gly Asp Leu Glu Leu Phe Asp Leu Val Glu Glu Val Gln Leu
      50          55          60

Asn Phe Tyr Gln Phe Leu Gly Val Gln Gln Asp Ala Ser Ser Ala Asp
      65          70          75          80

Ile Arg Lys Ala Tyr Arg Lys Leu Ser Leu Thr Leu His Pro Asp Lys
      85          90          95

Asn Lys Asp Glu Asn Ala Glu Thr Gln Phe Arg Gln Val Thr Thr Lys

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| 100                                                                                                                                                               | 105         | 110 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----|
| Ala Lys Gln Leu Lys Asp Ser Val Thr Cys Ser Pro Gly Met Val Arg<br>115 120 125                                                                                    |             |     |
| Leu Ser Glu Leu Lys Ser Thr Val Gln Asn Ser Arg Pro Ile Lys Thr<br>130 135 140                                                                                    |             |     |
| Ala Thr Thr Leu Pro Asp Asp Met Ile Thr Gln Arg Glu Asp Ala Glu<br>145 150 155 160                                                                                |             |     |
| Gly Val Ala Ala Glu Glu Glu Gln Glu Gly Asp Ser Gly Glu Gln Glu<br>165 170 175                                                                                    |             |     |
| Thr Gly Ala Thr Asp Ala Arg Pro Arg Arg Arg Lys Pro Ala Arg Leu<br>180 185 190                                                                                    |             |     |
| Leu Glu Ala Thr Ala Lys Pro Glu Pro Glu Glu Lys Ser Arg Ala Lys<br>195 200 205                                                                                    |             |     |
| Arg Gln Lys Asp Phe Asp Ile Ala Glu Gln Asn Glu Ser Ser Asp Glu<br>210 215 220                                                                                    |             |     |
| Glu Ser Leu Arg Lys Glu Arg Ala Arg Ser Ala Glu Glu Pro Trp Thr<br>225 230 235 240                                                                                |             |     |
| Gln Asn Gln Gln Lys Leu Leu Glu Leu Ala Leu Gln Gln Tyr Pro Arg<br>245 250 255                                                                                    |             |     |
| Gly Ser Ser Asp Arg Trp Asp Lys Ile Ala Arg Cys Val Pro Ser Lys<br>260 265 270                                                                                    |             |     |
| Ser Lys Glu Asp Cys Ile Ala Arg Tyr Lys Leu Leu Val Glu Leu Val<br>275 280 285                                                                                    |             |     |
| Gln Lys Lys Lys Gln Ala Lys Ser<br>290 295                                                                                                                        |             |     |
| <210> SEQ ID NO 17<br><211> LENGTH: 1881<br><212> TYPE: DNA<br><213> ORGANISM: human<br><220> FEATURE:<br><221> NAME/KEY: CDS<br><222> LOCATION: (108) ... (1772) |             |     |
| <400> SEQUENCE: 17                                                                                                                                                |             |     |
| gcgcttttca ctgacaggcg ctgttcccca cagccagcgc cgcccgcac gtcccagctc                                                                                                  | 60          |     |
| tcggccaacg gagctgcgcg gcgggtgacc tttccgagcc cagcgcg atg acg gct                                                                                                   | 116         |     |
|                                                                                                                                                                   | Met Thr Ala |     |
|                                                                                                                                                                   | 1           |     |
| cct tgc tcc cag ccg gcg cag ctt cct gga cgc cgc cag ctc ggg ctg                                                                                                   | 164         |     |
| Pro Cys Ser Gln Pro Ala Gln Leu Pro Gly Arg Arg Gln Leu Gly Leu                                                                                                   |             |     |
| 5 10 15                                                                                                                                                           |             |     |
| gtg ccg ttc ccg ccg ccg ccg ccg acg ccg ctg ctg tgg ctg ctg                                                                                                       | 212         |     |
| Val Pro Phe Pro Pro Pro Pro Pro Arg Thr Pro Leu Leu Trp Leu Leu                                                                                                   |             |     |
| 20 25 30 35                                                                                                                                                       |             |     |
| ctg ctg ctg ctg gcc gcc gtg gcg ccg gcg cgc gcc tgg gag agc gga                                                                                                   | 260         |     |
| Leu Leu Leu Leu Ala Ala Val Ala Pro Ala Arg Gly Trp Glu Ser Gly                                                                                                   |             |     |
| 40 45 50                                                                                                                                                          |             |     |
| gac ctg gag ttg ttt gac tta gtg gag gag gtg cag ctc aac ttc tac                                                                                                   | 308         |     |
| Asp Leu Glu Leu Phe Asp Leu Val Glu Glu Val Gln Leu Asn Phe Tyr                                                                                                   |             |     |
| 55 60 65                                                                                                                                                          |             |     |
| cag ttc ctc ggg gtg cag cag gat gca tca tct gca gac atc aga aaa                                                                                                   | 356         |     |
| Gln Phe Leu Gly Val Gln Gln Asp Ala Ser Ser Ala Asp Ile Arg Lys                                                                                                   |             |     |
| 70 75 80                                                                                                                                                          |             |     |
| gca tat cgt aag ctt tca cta act tta cat cca gac aag aat aaa gat                                                                                                   | 404         |     |

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| Ala | Tyr | Arg | Lys | Leu | Ser | Leu | Thr | Leu | His | Pro | Asp | Lys | Asn | Lys | Asp |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |     |     |     |      |
| gaa | aat | gca | gaa | act | cag | ttt | aga | caa | ttg | gtg | gcc | att | tat | gaa | gtt | 452  |
| Glu | Asn | Ala | Glu | Thr | Gln | Phe | Arg | Gln | Leu | Val | Ala | Ile | Tyr | Glu | Val |      |
| 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     | 115 |     |      |
| tta | aag | gat | gat | gaa | cga | agg | cag | agg | tat | gat | gat | att | ctg | atc | aat | 500  |
| Leu | Lys | Asp | Asp | Glu | Arg | Arg | Gln | Arg | Tyr | Asp | Asp | Ile | Leu | Ile | Asn |      |
|     |     |     |     | 120 |     |     |     |     | 125 |     |     |     | 130 |     |     |      |
| gga | ctt | cca | gat | tgg | cga | cag | cct | gta | ttc | tac | tac | agg | cgg | gtg | aga | 548  |
| Gly | Leu | Pro | Asp | Trp | Arg | Gln | Pro | Val | Phe | Tyr | Tyr | Arg | Arg | Val | Arg |      |
|     |     |     | 135 |     |     |     |     | 140 |     |     |     |     | 145 |     |     |      |
| aaa | atg | agc | aat | gct | gag | ctg | gca | tta | ctc | ttg | ttc | att | att | ctc | aca | 596  |
| Lys | Met | Ser | Asn | Ala | Glu | Leu | Ala | Leu | Leu | Leu | Phe | Ile | Ile | Leu | Thr |      |
|     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |     |     |     |      |
| gtg | ggt | cat | tat | gct | gtg | ggt | tgg | tca | atc | tac | ctg | gaa | aaa | caa | ctg | 644  |
| Val | Gly | His | Tyr | Ala | Val | Val | Trp | Ser | Ile | Tyr | Leu | Glu | Lys | Gln | Leu |      |
|     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     |      |
| gat | gaa | cta | cta | agt | aga | aaa | aag | aga | gaa | aag | aaa | aaa | aag | act | ggc | 692  |
| Asp | Glu | Leu | Leu | Ser | Arg | Lys | Lys | Arg | Glu | Lys | Lys | Lys | Lys | Thr | Gly |      |
| 180 |     |     |     |     | 185 |     |     |     | 190 |     |     |     |     | 195 |     |      |
| agc | aag | agt | gtg | gat | gta | tca | aaa | ctc | ggt | gct | tca | gaa | aaa | aat | gaa | 740  |
| Ser | Lys | Ser | Val | Asp | Val | Ser | Lys | Leu | Gly | Ala | Ser | Glu | Lys | Asn | Glu |      |
|     |     |     | 200 |     |     |     |     |     | 205 |     |     |     |     | 210 |     |      |
| aga | ttg | ctg | atg | aaa | cca | cag | tgg | cat | gat | ttg | ctt | cca | tgc | aaa | ctg | 788  |
| Arg | Leu | Leu | Met | Lys | Pro | Gln | Trp | His | Asp | Leu | Leu | Pro | Cys | Lys | Leu |      |
|     |     |     | 215 |     |     |     |     | 220 |     |     |     |     | 225 |     |     |      |
| ggg | att | tgg | ttt | tgc | ctt | aca | cta | aaa | gca | tta | cct | cac | ctc | atc | cag | 836  |
| Gly | Ile | Trp | Phe | Cys | Leu | Thr | Leu | Lys | Ala | Leu | Pro | His | Leu | Ile | Gln |      |
|     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |     |     |      |
| gat | gct | ggg | cag | ttt | tat | gct | aaa | tat | aaa | gaa | aca | aga | ttg | aag | gaa | 884  |
| Asp | Ala | Gly | Gln | Phe | Tyr | Ala | Lys | Tyr | Lys | Glu | Thr | Arg | Leu | Lys | Glu |      |
|     | 245 |     |     |     |     | 250 |     |     |     | 255 |     |     |     |     |     |      |
| aag | gaa | gat | gca | ctg | act | aga | act | gaa | ctt | gaa | aca | ctt | caa | aaa | cag | 932  |
| Lys | Glu | Asp | Ala | Leu | Thr | Arg | Thr | Glu | Leu | Glu | Thr | Leu | Gln | Lys | Gln |      |
|     | 260 |     |     |     | 265 |     |     |     | 270 |     |     |     |     | 275 |     |      |
| aag | aaa | gtt | aaa | aaa | cca | aaa | cct | gaa | ttt | cct | gta | tac | aca | cct | tta | 980  |
| Lys | Lys | Val | Lys | Lys | Pro | Lys | Pro | Glu | Phe | Pro | Val | Tyr | Thr | Pro | Leu |      |
|     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     | 290 |     |      |
| gaa | act | aca | tat | att | cag | tct | tat | gat | cat | gga | act | tcc | ata | gaa | gaa | 1028 |
| Glu | Thr | Thr | Tyr | Ile | Gln | Ser | Tyr | Asp | His | Gly | Thr | Ser | Ile | Glu | Glu |      |
|     |     |     | 295 |     |     |     |     | 300 |     |     |     |     | 305 |     |     |      |
| att | gag | gaa | caa | atg | gat | gat | tgg | ttg | gaa | aac | agg | aac | cga | aca | cag | 1076 |
| Ile | Glu | Glu | Gln | Met | Asp | Asp | Trp | Leu | Glu | Asn | Arg | Asn | Arg | Thr | Gln |      |
|     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |     |     |     |      |
| aaa | aaa | cag | gca | cct | gaa | tgg | aca | gaa | gag | gac | ctc | agc | caa | ctg | aca | 1124 |
| Lys | Lys | Gln | Ala | Pro | Glu | Trp | Thr | Glu | Glu | Asp | Leu | Ser | Gln | Leu | Thr |      |
|     |     | 325 |     |     |     | 330 |     |     |     | 335 |     |     |     |     |     |      |
| aga | agt | atg | gtt | aag | ttc | cca | gga | ggg | act | cca | ggt | cga | tgg | gaa | aag | 1172 |
| Arg | Ser | Met | Val | Lys | Phe | Pro | Gly | Gly | Thr | Pro | Gly | Arg | Trp | Glu | Lys |      |
|     | 340 |     |     |     | 345 |     |     |     | 350 |     |     |     |     | 355 |     |      |
| att | gcc | cac | gaa | ttg | ggt | cga | tct | gtg | aca | gat | gtg | aca | acc | aaa | gcc | 1220 |
| Ile | Ala | His | Glu | Leu | Gly | Arg | Ser | Val | Thr | Asp | Val | Thr | Thr | Lys | Ala |      |
|     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |     | 370 |     |      |
| aag | caa | ctg | aag | gat | tca | gtg | acc | tgc | tcc | cca | gga | atg | gtt | aga | ctc | 1268 |
| Lys | Gln | Leu | Lys | Asp | Ser | Val | Thr | Cys | Ser | Pro | Gly | Met | Val | Arg | Leu |      |
|     |     | 375 |     |     |     |     |     | 380 |     |     |     |     | 385 |     |     |      |
| tcc | gaa | ctc | aaa | tcg | aca | gtt | cag | aat | tcc | agg | ccc | atc | aaa | acg | gcc | 1316 |

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|            |            |            |            |            |            |      |     |            |            |            |      |     |      |     |     |      |  |
|------------|------------|------------|------------|------------|------------|------|-----|------------|------------|------------|------|-----|------|-----|-----|------|--|
| Ser        | Glu        | Leu        | Lys        | Ser        | Thr        | Val  | Gln | Asn        | Ser        | Arg        | Pro  | Ile | Lys  | Thr | Ala |      |  |
|            |            | 390        |            |            |            |      | 395 |            |            |            |      | 400 |      |     |     |      |  |
| acc        | acc        | ttg        | ccc        | gat        | gac        | atg  | atc | acc        | cag        | cga        | gag  | gac | gca  | gag | ggg | 1364 |  |
| Thr        | Thr        | Leu        | Pro        | Asp        | Asp        | Met  | Ile | Thr        | Gln        | Arg        | Glu  | Asp | Ala  | Glu | Gly |      |  |
|            |            | 405        |            |            |            | 410  |     |            |            | 415        |      |     |      |     |     |      |  |
| gtg        | gca        | gcg        | gag        | gag        | gag        | cag  | gag | gga        | gac        | tcc        | ggt  | gag | cag  | gag | acc | 1412 |  |
| Val        | Ala        | Ala        | Glu        | Glu        | Glu        | Gln  | Glu | Gly        | Asp        | Ser        | Gly  | Glu | Gln  | Glu | Thr |      |  |
|            |            | 420        |            |            | 425        |      |     |            | 430        |            |      |     |      | 435 |     |      |  |
| ggg        | gcc        | act        | gat        | gcc        | cgg        | cct  | cgg | agg        | cgg        | aag        | cca  | gcc | agg  | ctg | ctg | 1460 |  |
| Gly        | Ala        | Thr        | Asp        | Ala        | Arg        | Pro  | Arg | Arg        | Arg        | Lys        | Pro  | Ala | Arg  | Leu | Leu |      |  |
|            |            |            | 440        |            |            |      |     | 445        |            |            |      |     |      | 450 |     |      |  |
| gag        | gct        | aca        | gcg        | aag        | ccg        | gag  | cca | gag        | gag        | aag        | tcc  | aga | gcc  | aag | cgg | 1508 |  |
| Glu        | Ala        | Thr        | Ala        | Lys        | Pro        | Glu  | Pro | Glu        | Glu        | Lys        | Ser  | Arg | Ala  | Lys | Arg |      |  |
|            |            |            | 455        |            |            |      |     | 460        |            |            |      |     | 465  |     |     |      |  |
| cag        | aag        | gac        | ttt        | gac        | ata        | gca  | gaa | caa        | aac        | gag        | tcc  | agc | gac  | gag | gag | 1556 |  |
| Gln        | Lys        | Asp        | Phe        | Asp        | Ile        | Ala  | Glu | Gln        | Asn        | Glu        | Ser  | Ser | Asp  | Glu | Glu |      |  |
|            |            | 470        |            |            |            | 475  |     |            |            | 480        |      |     |      |     |     |      |  |
| agc        | ctg        | aga        | aaa        | gag        | aga        | gct  | cgg | tct        | gca        | gag        | gag  | ccg | tggt | act | caa | 1604 |  |
| Ser        | Leu        | Arg        | Lys        | Glu        | Arg        | Ala  | Arg | Ser        | Ala        | Glu        | Glu  | Pro | Trp  | Thr | Gln |      |  |
|            |            | 485        |            |            |            | 490  |     |            |            | 495        |      |     |      |     |     |      |  |
| aat        | caa        | cag        | aaa        | ctt        | ctg        | gaa  | ctg | gcg        | ttg        | cag        | cag  | tac | cca  | agg | gga | 1652 |  |
| Asn        | Gln        | Gln        | Lys        | Leu        | Leu        | Glu  | Leu | Ala        | Leu        | Gln        | Gln  | Tyr | Pro  | Arg | Gly |      |  |
|            |            | 500        |            |            | 505        |      |     |            | 510        |            |      |     |      |     | 515 |      |  |
| tcc        | tct        | gac        | cg         | tg         | gac        | aaa  | ata | gcc        | aga        | tgt        | gtc  | ccg | tcc  | aag | agc | 1700 |  |
| Ser        | Ser        | Asp        | Arg        | Trp        | Asp        | Lys  | Ile | Ala        | Arg        | Cys        | Val  | Pro | Ser  | Lys | Ser |      |  |
|            |            |            | 520        |            |            |      |     | 525        |            |            |      |     | 530  |     |     |      |  |
| aag        | gaa        | gac        | tgt        | atc        | gct        | agg  | tac | aag        | ttg        | ctg        | gtt  | gaa | ctg  | gtc | caa | 1748 |  |
| Lys        | Glu        | Asp        | Cys        | Ile        | Ala        | Arg  | Tyr | Lys        | Leu        | Leu        | Val  | Glu | Leu  | Val | Gln |      |  |
|            |            | 535        |            |            |            | 540  |     |            |            |            |      | 545 |      |     |     |      |  |
| aag        | aaa        | aaa        | caa        | gct        | aaa        | agc  | tga | atattctggg | agatgatgtt | caccttcatt | 1802 |     |      |     |     |      |  |
| Lys        | Lys        | Lys        | Gln        | Ala        | Lys        | Ser  | *   |            |            |            |      |     |      |     |     |      |  |
|            |            | 550        |            |            |            |      |     |            |            |            |      |     |      |     |     |      |  |
| ttccaaaatg | aatatcttaa | aaatcttatg | cagaaatttg | cattttgtac | ctcaatattt | 1862 |     |            |            |            |      |     |      |     |     |      |  |
| ctacgtcatg | tgccctagt  | 1881       |            |            |            |      |     |            |            |            |      |     |      |     |     |      |  |

<210> SEQ ID NO 18  
 <211> LENGTH: 554  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 18

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
| Met | Thr | Ala | Pro | Cys | Ser | Gln | Pro | Ala | Gln | Leu | Pro | Gly | Arg | Arg | Gln |  |  |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |  |
| Leu | Gly | Leu | Val | Pro | Phe | Pro | Pro | Pro | Pro | Arg | Thr | Pro | Leu | Leu |     |  |  |
|     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |     |  |  |
| Trp | Leu | Leu | Leu | Leu | Leu | Ala | Ala | Val | Ala | Pro | Ala | Arg | Gly | Trp |     |  |  |
|     |     | 35  |     |     |     | 40  |     |     |     | 45  |     |     |     |     |     |  |  |
| Glu | Ser | Gly | Asp | Leu | Glu | Leu | Phe | Asp | Leu | Val | Glu | Glu | Val | Gln | Leu |  |  |
|     |     | 50  |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |  |  |
| Asn | Phe | Tyr | Gln | Phe | Leu | Gly | Val | Gln | Gln | Asp | Ala | Ser | Ser | Ala | Asp |  |  |
|     |     | 65  |     |     | 70  |     |     |     | 75  |     |     |     |     | 80  |     |  |  |
| Ile | Arg | Lys | Ala | Tyr | Arg | Lys | Leu | Ser | Leu | Thr | Leu | His | Pro | Asp | Lys |  |  |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |     | 95  |     |  |  |
| Asn | Lys | Asp | Glu | Asn | Ala | Glu | Thr | Gln | Phe | Arg | Gln | Leu | Val | Ala | Ile |  |  |
|     |     | 100 |     |     |     |     |     | 105 |     |     |     |     |     | 110 |     |  |  |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Glu | Val | Leu | Lys | Asp | Asp | Glu | Arg | Arg | Gln | Arg | Tyr | Asp | Asp | Ile |
|     | 115 |     |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Leu | Ile | Asn | Gly | Leu | Pro | Asp | Trp | Arg | Gln | Pro | Val | Phe | Tyr | Tyr | Arg |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Arg | Val | Arg | Lys | Met | Ser | Asn | Ala | Glu | Leu | Ala | Leu | Leu | Leu | Phe | Ile |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Ile | Leu | Thr | Val | Gly | His | Tyr | Ala | Val | Val | Trp | Ser | Ile | Tyr | Leu | Glu |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Lys | Gln | Leu | Asp | Glu | Leu | Leu | Ser | Arg | Lys | Lys | Arg | Glu | Lys | Lys | Lys |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Lys | Thr | Gly | Ser | Lys | Ser | Val | Asp | Val | Ser | Lys | Leu | Gly | Ala | Ser | Glu |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Lys | Asn | Glu | Arg | Leu | Leu | Met | Lys | Pro | Gln | Trp | His | Asp | Leu | Leu | Pro |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Cys | Lys | Leu | Gly | Ile | Trp | Phe | Cys | Leu | Thr | Leu | Lys | Ala | Leu | Pro | His |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Leu | Ile | Gln | Asp | Ala | Gly | Gln | Phe | Tyr | Ala | Lys | Tyr | Lys | Glu | Thr | Arg |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Leu | Lys | Glu | Lys | Glu | Asp | Ala | Leu | Thr | Arg | Thr | Glu | Leu | Glu | Thr | Leu |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Gln | Lys | Gln | Lys | Lys | Val | Lys | Lys | Pro | Lys | Pro | Glu | Phe | Pro | Val | Tyr |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Thr | Pro | Leu | Glu | Thr | Thr | Tyr | Ile | Gln | Ser | Tyr | Asp | His | Gly | Thr | Ser |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ile | Glu | Glu | Ile | Glu | Glu | Gln | Met | Asp | Asp | Trp | Leu | Glu | Asn | Arg | Asn |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Arg | Thr | Gln | Lys | Lys | Gln | Ala | Pro | Glu | Trp | Thr | Glu | Glu | Asp | Leu | Ser |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Gln | Leu | Thr | Arg | Ser | Met | Val | Lys | Phe | Pro | Gly | Gly | Thr | Pro | Gly | Arg |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Trp | Glu | Lys | Ile | Ala | His | Glu | Leu | Gly | Arg | Ser | Val | Thr | Asp | Val | Thr |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Thr | Lys | Ala | Lys | Gln | Leu | Lys | Asp | Ser | Val | Thr | Cys | Ser | Pro | Gly | Met |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Val | Arg | Leu | Ser | Glu | Leu | Lys | Ser | Thr | Val | Gln | Asn | Ser | Arg | Pro | Ile |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Lys | Thr | Ala | Thr | Thr | Leu | Pro | Asp | Asp | Met | Ile | Thr | Gln | Arg | Glu | Asp |
|     |     |     | 405 |     |     |     |     | 410 |     |     |     |     |     | 415 |     |
| Ala | Glu | Gly | Val | Ala | Ala | Glu | Glu | Glu | Gln | Glu | Gly | Asp | Ser | Gly | Glu |
|     |     | 420 |     |     |     |     | 425 |     |     |     |     |     | 430 |     |     |
| Gln | Glu | Thr | Gly | Ala | Thr | Asp | Ala | Arg | Pro | Arg | Arg | Arg | Lys | Pro | Ala |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Arg | Leu | Leu | Glu | Ala | Thr | Ala | Lys | Pro | Glu | Pro | Glu | Glu | Lys | Ser | Arg |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Lys | Arg | Gln | Lys | Asp | Phe | Asp | Ile | Ala | Glu | Gln | Asn | Glu | Ser | Ser |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Asp | Glu | Glu | Ser | Leu | Arg | Lys | Glu | Arg | Ala | Arg | Ser | Ala | Glu | Glu | Pro |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Trp | Thr | Gln | Asn | Gln | Gln | Lys | Leu | Leu | Glu | Leu | Ala | Leu | Gln | Gln | Tyr |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Pro | Arg | Gly | Ser | Ser | Asp | Arg | Trp | Asp | Lys | Ile | Ala | Arg | Cys | Val | Pro |

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| 515                                                               | 520 | 525         |      |
|-------------------------------------------------------------------|-----|-------------|------|
| Ser Lys Ser Lys Glu Asp Cys Ile Ala Arg Tyr Lys Leu Leu Val Glu   |     |             |      |
| 530                                                               | 535 | 540         |      |
| Leu Val Gln Lys Lys Lys Gln Ala Lys Ser                           |     |             |      |
| 545                                                               | 550 |             |      |
| <br><210> SEQ ID NO 19                                            |     |             |      |
| <211> LENGTH: 4252                                                |     |             |      |
| <212> TYPE: DNA                                                   |     |             |      |
| <213> ORGANISM: human                                             |     |             |      |
| <220> FEATURE:                                                    |     |             |      |
| <221> NAME/KEY: CDS                                               |     |             |      |
| <222> LOCATION: (528) ... (3053)                                  |     |             |      |
| <br><400> SEQUENCE: 19                                            |     |             |      |
| tttatttacg cctacctccc agcccttggc aatctgacta ataacaaact gagctaacaa |     |             | 60   |
| gaaatactag aaaaggagga aggagaacat tgctgtagct tggatctaca acctaagaaa |     |             | 120  |
| gcaagagtga tcaatctcag ctctgttaaa catcttggtt acttactgca ttcagcagct |     |             | 180  |
| tgcaaatggt taactatatg caaaaaagtc agcatagctg tgaagtatgc cgtgaatttt |     |             | 240  |
| aattgagggg aaaaggggaca attgcttcag gatgctctag tatgcactct gcttgaata |     |             | 300  |
| ttttcaatga aatgctcagt attctatctt tgaccagagg ttttaacttt atgaagctat |     |             | 360  |
| gggacttgac aaaaagtgat atttgagaag aaagtacgca gtggttggtg ttttcttttt |     |             | 420  |
| tttaataaag gaattgaatt actttgaaca cctcttcag ctgtgcatta cagataacgt  |     |             | 480  |
| caggaagagt ctctgcttta cagaatcgga tttcatcaca tgacaac atg aag ctg   |     |             | 536  |
|                                                                   |     | Met Lys Leu |      |
|                                                                   |     | 1           |      |
| tggtt att cat ctc ttt tat tca tct ctc ctt gcc tgt ata tct tta cac |     |             | 584  |
| Trp Ile His Leu Phe Tyr Ser Ser Leu Leu Ala Cys Ile Ser Leu His   |     |             |      |
| 5                                                                 | 10  | 15          |      |
| tcc caa act cca gtg ctc tca tcc aga ggc tct tgt gat tct ctt tgc   |     |             | 632  |
| Ser Gln Thr Pro Val Leu Ser Ser Arg Gly Ser Cys Asp Ser Leu Cys   |     |             |      |
| 20                                                                | 25  | 30          | 35   |
| aat tgt gag gaa aaa gat ggc aca atg cta ata aat tgt gaa gca aaa   |     |             | 680  |
| Asn Cys Glu Glu Lys Asp Gly Thr Met Leu Ile Asn Cys Glu Ala Lys   |     |             |      |
|                                                                   | 40  | 45          | 50   |
| ggt atc aag atg gta tct gaa ata agt gtg cca cca tca cga cct ttc   |     |             | 728  |
| Gly Ile Lys Met Val Ser Glu Ile Ser Val Pro Pro Ser Arg Pro Phe   |     |             |      |
|                                                                   | 55  | 60          | 65   |
| caa cta agc tta tta aat aac ggc ttg acg atg ctt cac aca aat gac   |     |             | 776  |
| Gln Leu Ser Leu Leu Asn Asn Gly Leu Thr Met Leu His Thr Asn Asp   |     |             |      |
|                                                                   | 70  | 75          | 80   |
| ttt tct ggg ctt acc aat gct att tca ata cac ctt gga ttt aac aat   |     |             | 824  |
| Phe Ser Gly Leu Thr Asn Ala Ile Ser Ile His Leu Gly Phe Asn Asn   |     |             |      |
|                                                                   | 85  | 90          | 95   |
| att gca gat att gag ata ggt gca ttt aat ggc ctt ggc ctc ctg aaa   |     |             | 872  |
| Ile Ala Asp Ile Glu Ile Gly Ala Phe Asn Gly Leu Gly Leu Leu Lys   |     |             |      |
|                                                                   | 100 | 105         | 110  |
| caa ctt cat atc aat cac aat tct tta gaa att ctt aaa gag gat act   |     |             | 920  |
| Gln Leu His Ile Asn His Asn Ser Leu Glu Ile Leu Lys Glu Asp Thr   |     |             |      |
|                                                                   | 120 | 125         | 130  |
| ttc cat gga ctg gaa aac ctg gaa ttc ctg caa gca gat aac aat ttt   |     |             | 968  |
| Phe His Gly Leu Glu Asn Leu Glu Phe Leu Gln Ala Asp Asn Asn Phe   |     |             |      |
|                                                                   | 135 | 140         | 145  |
| atc aca gtg att gaa cca agt gcc ttt agc aag ctc aac aga ctc aaa   |     |             | 1016 |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Ile | Thr | Val | Ile | Glu | Pro | Ser | Ala | Phe | Ser | Lys | Leu | Asn | Arg | Leu | Lys |      |
|     | 150 |     |     |     |     |     | 155 |     |     |     |     | 160 |     |     |     |      |
| gtg | tta | att | tta | aat | gac | aat | gct | att | gag | agt | ctt | cct | cca | aac | atc | 1064 |
| Val | Leu | Ile | Leu | Asn | Asp | Asn | Ala | Ile | Glu | Ser | Leu | Pro | Pro | Asn | Ile |      |
|     | 165 |     |     |     |     |     | 170 |     |     |     | 175 |     |     |     |     |      |
| ttc | cga | ttt | gtt | cct | tta | acc | cat | cta | gat | ctt | cgt | gga | aat | caa | tta | 1112 |
| Phe | Arg | Phe | Val | Pro | Leu | Thr | His | Leu | Asp | Leu | Arg | Gly | Asn | Gln | Leu |      |
|     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     | 195 |      |
| caa | aca | ttg | cct | tat | gtt | ggg | ttt | ctc | gaa | cac | att | ggc | cga | ata | ttg | 1160 |
| Gln | Thr | Leu | Pro | Tyr | Val | Gly | Phe | Leu | Glu | His | Ile | Gly | Arg | Ile | Leu |      |
|     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     | 210 |     |      |
| gat | ctt | cag | ttg | gag | gac | aac | aaa | tgg | gcc | tgc | aat | tgt | gac | tta | ttg | 1208 |
| Asp | Leu | Gln | Leu | Glu | Asp | Asn | Lys | Trp | Ala | Cys | Asn | Cys | Asp | Leu | Leu |      |
|     |     | 215 |     |     |     |     |     | 220 |     |     |     | 225 |     |     |     |      |
| cag | tta | aaa | act | tgg | ttg | gag | aac | atg | cct | cca | cag | tct | ata | att | ggg | 1256 |
| Gln | Leu | Lys | Thr | Trp | Leu | Glu | Asn | Met | Pro | Pro | Gln | Ser | Ile | Ile | Gly |      |
|     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |     |     |      |
| gat | gtt | gtc | tgc | aac | agc | cct | cca | ttt | ttt | aaa | gga | agt | ata | ctc | agt | 1304 |
| Asp | Val | Val | Cys | Asn | Ser | Pro | Pro | Phe | Phe | Lys | Gly | Ser | Ile | Leu | Ser |      |
|     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |     |     |      |
| aga | cta | aag | aag | gaa | tct | att | tgc | cct | act | cca | cca | gtg | tat | gaa | gaa | 1352 |
| Arg | Leu | Lys | Lys | Glu | Ser | Ile | Cys | Pro | Thr | Pro | Pro | Val | Tyr | Glu | Glu |      |
|     | 260 |     |     |     | 265 |     |     |     | 270 |     |     |     |     | 275 |     |      |
| cat | gag | gat | cct | tca | gga | tca | tta | cat | ctg | gca | gca | aca | tct | tca | ata | 1400 |
| His | Glu | Asp | Pro | Ser | Gly | Ser | Leu | His | Leu | Ala | Ala | Thr | Ser | Ser | Ile |      |
|     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     | 290 |     |      |
| aat | gat | agt | cgc | atg | tca | act | aag | acc | acg | tcc | att | cta | aaa | cta | ccc | 1448 |
| Asn | Asp | Ser | Arg | Met | Ser | Thr | Lys | Thr | Thr | Ser | Ile | Leu | Lys | Leu | Pro |      |
|     |     | 295 |     |     |     |     |     | 300 |     |     |     |     | 305 |     |     |      |
| acc | aaa | gca | cca | ggg | ttg | ata | cct | tat | att | aca | aag | cca | tcc | act | caa | 1496 |
| Thr | Lys | Ala | Pro | Gly | Leu | Ile | Pro | Tyr | Ile | Thr | Lys | Pro | Ser | Thr | Gln |      |
|     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |     |     |     |      |
| ctt | cca | gga | cct | tac | tgc | cct | att | cct | tgt | aac | tgc | aaa | gtc | cta | tcc | 1544 |
| Leu | Pro | Gly | Pro | Tyr | Cys | Pro | Ile | Pro | Cys | Asn | Cys | Lys | Val | Leu | Ser |      |
|     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |     |     |      |
| cca | tca | gga | ctt | cta | ata | cat | tgt | cag | gag | cgc | aac | att | gaa | agc | tta | 1592 |
| Pro | Ser | Gly | Leu | Leu | Ile | His | Cys | Gln | Glu | Arg | Asn | Ile | Glu | Ser | Leu |      |
|     | 340 |     |     |     | 345 |     |     |     | 350 |     |     |     |     | 355 |     |      |
| tca | gat | ctg | aga | cct | cct | ccg | caa | aat | cct | aga | aag | ctc | att | cta | gcg | 1640 |
| Ser | Asp | Leu | Arg | Pro | Pro | Pro | Gln | Asn | Pro | Arg | Lys | Leu | Ile | Leu | Ala |      |
|     |     | 360 |     |     |     |     |     |     | 365 |     |     |     |     | 370 |     |      |
| gga | aat | att | att | cac | agt | tta | atg | aag | tct | gat | cta | gtg | gaa | tat | ttc | 1688 |
| Gly | Asn | Ile | Ile | His | Ser | Leu | Met | Lys | Ser | Asp | Leu | Val | Glu | Tyr | Phe |      |
|     |     | 375 |     |     |     |     |     | 380 |     |     |     |     | 385 |     |     |      |
| act | ttg | gaa | atg | ctt | cac | ttg | gga | aac | aat | cgt | att | gaa | gtt | ctt | gaa | 1736 |
| Thr | Leu | Glu | Met | Leu | His | Leu | Gly | Asn | Asn | Arg | Ile | Glu | Val | Leu | Glu |      |
|     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |     |     |     |      |
| gaa | gga | tcg | ttt | atg | aac | cta | acg | aga | tta | caa | aaa | ctc | tat | cta | aat | 1784 |
| Glu | Gly | Ser | Phe | Met | Asn | Leu | Thr | Arg | Leu | Gln | Lys | Leu | Tyr | Leu | Asn |      |
|     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |     |     |     |      |
| ggg | aac | cac | ctg | acc | aaa | tta | agt | aaa | ggc | atg | ttc | ctt | ggg | ctc | cat | 1832 |
| Gly | Asn | His | Leu | Thr | Lys | Leu | Ser | Lys | Gly | Met | Phe | Leu | Gly | Leu | His |      |
|     | 420 |     |     |     | 425 |     |     |     | 430 |     |     |     |     | 435 |     |      |
| aat | ctt | gaa | tac | tta | tat | ctt | gaa | tac | aat | gcc | att | aag | gaa | ata | ctg | 1880 |
| Asn | Leu | Glu | Tyr | Leu | Tyr | Leu | Glu | Tyr | Asn | Ala | Ile | Lys | Glu | Ile | Leu |      |
|     |     |     | 440 |     |     |     |     | 445 |     |     |     |     |     | 450 |     |      |
| cca | gga | acc | ttt | aat | cca | atg | cct | aaa | ctt | aaa | gtc | ctg | tat | tta | aat | 1928 |

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| Pro | Gly | Thr | Phe | Asn | Pro | Met | Pro | Lys | Leu | Lys | Val | Leu | Tyr | Leu | Asn |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|     |     |     | 455 |     |     |     |     | 460 |     |     |     |     | 465 |     |     |      |
| aac | aac | ctc | ctc | caa | gtt | tta | cca | cca | cat | att | ttt | tca | ggg | gtt | cct | 1976 |
| Asn | Asn | Leu | Leu | Gln | Val | Leu | Pro | Pro | His | Ile | Phe | Ser | Gly | Val | Pro |      |
|     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |     |     |     |      |
| cta | act | aag | gta | aat | ctt | aaa | aca | aac | cag | ttt | acc | cat | cta | cct | gta | 2024 |
| Leu | Thr | Lys | Val | Asn | Leu | Lys | Thr | Asn | Gln | Phe | Thr | His | Leu | Pro | Val |      |
|     |     | 485 |     |     |     | 490 |     |     |     |     | 495 |     |     |     |     |      |
| agt | aat | att | ttg | gat | gat | ctt | gat | tta | cta | acc | cag | att | gac | ctt | gag | 2072 |
| Ser | Asn | Ile | Leu | Asp | Asp | Leu | Asp | Leu | Leu | Thr | Gln | Ile | Asp | Leu | Glu |      |
| 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |     | 515 |     |      |
| gat | aac | ccc | tgg | gac | tgc | tcc | tgt | gac | ctg | gtt | gga | ctg | cag | caa | tgg | 2120 |
| Asp | Asn | Pro | Trp | Asp | Cys | Ser | Cys | Asp | Leu | Val | Gly | Leu | Gln | Gln | Trp |      |
|     |     |     | 520 |     |     |     |     | 525 |     |     |     |     |     | 530 |     |      |
| ata | caa | aag | tta | agc | aag | aac | aca | gtg | aca | gat | gac | atc | ctc | tgc | act | 2168 |
| Ile | Gln | Lys | Leu | Ser | Lys | Asn | Thr | Val | Thr | Asp | Asp | Ile | Leu | Cys | Thr |      |
|     |     |     | 535 |     |     |     |     | 540 |     |     |     |     | 545 |     |     |      |
| tcc | ccc | ggg | cat | ctc | gac | aaa | aag | gaa | ttg | aaa | gcc | cta | aat | agt | gaa | 2216 |
| Ser | Pro | Gly | His | Leu | Asp | Lys | Lys | Glu | Leu | Lys | Ala | Leu | Asn | Ser | Glu |      |
|     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |     |     |     |      |
| att | ctc | tgt | cca | ggg | tta | gta | aat | aac | cca | tcc | atg | cca | aca | cag | act | 2264 |
| Ile | Leu | Cys | Pro | Gly | Leu | Val | Asn | Asn | Pro | Ser | Met | Pro | Thr | Gln | Thr |      |
|     |     | 565 |     |     |     | 570 |     |     |     |     | 575 |     |     |     |     |      |
| agt | tac | ctt | atg | gtc | acc | act | cct | gca | aca | aca | aca | aat | acg | gct | gat | 2312 |
| Ser | Tyr | Leu | Met | Val | Thr | Thr | Pro | Ala | Thr | Thr | Thr | Asn | Thr | Ala | Asp |      |
| 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |     | 595 |     |      |
| act | att | tta | cga | tct | ctt | acg | gac | gct | gtg | cca | ctg | tct | gtt | cta | ata | 2360 |
| Thr | Ile | Leu | Arg | Ser | Leu | Thr | Asp | Ala | Val | Pro | Leu | Ser | Val | Leu | Ile |      |
|     |     |     | 600 |     |     |     |     | 605 |     |     |     |     |     | 610 |     |      |
| ttg | gga | ctt | ctg | att | atg | ttc | atc | act | att | gtt | ttc | tgt | gct | gca | ggg | 2408 |
| Leu | Gly | Leu | Leu | Ile | Met | Phe | Ile | Thr | Ile | Val | Phe | Cys | Ala | Ala | Gly |      |
|     |     | 615 |     |     |     |     |     | 620 |     |     |     |     | 625 |     |     |      |
| ata | gtg | gtt | ctt | gtt | ctt | cac | cgc | agg | aga | aga | tac | aaa | aag | aaa | caa | 2456 |
| Ile | Val | Val | Leu | Val | Leu | His | Arg | Arg | Arg | Arg | Tyr | Lys | Lys | Lys | Gln |      |
|     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |     |     |     |      |
| gta | gat | gag | caa | atg | aga | gac | aac | agt | cct | gtg | cat | ctt | cag | tac | agc | 2504 |
| Val | Asp | Glu | Gln | Met | Arg | Asp | Asn | Ser | Pro | Val | His | Leu | Gln | Tyr | Ser |      |
|     |     | 645 |     |     |     | 650 |     |     |     |     | 655 |     |     |     |     |      |
| atg | tat | ggc | cat | aaa | acc | act | cat | cac | act | act | gaa | aga | ccc | tct | gcc | 2552 |
| Met | Tyr | Gly | His | Lys | Thr | Thr | His | His | Thr | Thr | Glu | Arg | Pro | Ser | Ala |      |
| 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |     | 675 |     |      |
| tca | ctc | tat | gaa | cag | cac | atg | gtg | agc | ccc | atg | gtt | cat | gtc | tat | aga | 2600 |
| Ser | Leu | Tyr | Glu | Gln | His | Met | Val | Ser | Pro | Met | Val | His | Val | Tyr | Arg |      |
|     |     |     | 680 |     |     |     |     |     | 685 |     |     |     |     | 690 |     |      |
| agt | cca | tcc | ttt | ggg | cca | aag | cat | ctg | gaa | gag | gaa | gaa | gag | agg | aat | 2648 |
| Ser | Pro | Ser | Phe | Gly | Pro | Lys | His | Leu | Glu | Glu | Glu | Glu | Glu | Arg | Asn |      |
|     |     |     | 695 |     |     |     |     | 700 |     |     |     |     | 705 |     |     |      |
| gag | aaa | gaa | gga | agt | gat | gca | aaa | cat | ctc | caa | aga | agt | ctt | ttg | gaa | 2696 |
| Glu | Lys | Glu | Gly | Ser | Asp | Ala | Lys | His | Leu | Gln | Arg | Ser | Leu | Leu | Glu |      |
|     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |     |     |     |      |
| cag | gaa | aat | cat | tca | cca | ctc | aca | ggg | tca | aat | atg | aaa | tac | aaa | acc | 2744 |
| Gln | Glu | Asn | His | Ser | Pro | Leu | Thr | Gly | Ser | Asn | Met | Lys | Tyr | Lys | Thr |      |
|     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |     |     |      |
| acg | aac | caa | tca | aca | gaa | ttt | tta | tcc | ttc | caa | gat | gcc | agc | tca | ttg | 2792 |
| Thr | Asn | Gln | Ser | Thr | Glu | Phe | Leu | Ser | Phe | Gln | Asp | Ala | Ser | Ser | Leu |      |
|     |     | 740 |     |     |     | 745 |     |     |     | 750 |     |     |     | 755 |     |      |
| tac | aga | aac | att | tta | gaa | aaa | gaa | agg | gaa | ctt | cag | caa | ctg | gga | atc | 2840 |

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|            |             |             |             |            |            |     |            |            |             |     |     |     |     |     |     |      |  |
|------------|-------------|-------------|-------------|------------|------------|-----|------------|------------|-------------|-----|-----|-----|-----|-----|-----|------|--|
| Tyr        | Arg         | Asn         | Ile         | Leu        | Glu        | Lys | Glu        | Arg        | Glu         | Leu | Gln | Gln | Leu | Gly | Ile |      |  |
|            |             |             |             | 760        |            |     |            |            | 765         |     |     |     |     | 770 |     |      |  |
| aca        | gaa         | tac         | cta         | agg        | aaa        | aac | att        | gct        | cag         | ctc | cag | cct | gat | atg | gag | 2888 |  |
| Thr        | Glu         | Tyr         | Leu         | Arg        | Lys        | Asn | Ile        | Ala        | Gln         | Leu | Gln | Pro | Asp | Met | Glu |      |  |
|            |             |             | 775         |            |            |     |            | 780        |             |     |     |     | 785 |     |     |      |  |
| gca        | cat         | tat         | cct         | gga        | gcc        | cac | gaa        | gag        | ctg         | aag | tta | atg | gaa | aca | tta | 2936 |  |
| Ala        | His         | Tyr         | Pro         | Gly        | Ala        | His | Glu        | Glu        | Leu         | Lys | Leu | Met | Glu | Thr | Leu |      |  |
|            |             |             | 790         |            |            |     | 795        |            |             |     |     | 800 |     |     |     |      |  |
| atg        | tac         | tca         | cgt         | cca        | agg        | aag | gta        | tta        | gtg         | gaa | cag | aca | aaa | aat | gag | 2984 |  |
| Met        | Tyr         | Ser         | Arg         | Pro        | Arg        | Lys | Val        | Leu        | Val         | Glu | Gln | Thr | Lys | Asn | Glu |      |  |
|            |             |             | 805         |            |            |     | 810        |            |             |     |     | 815 |     |     |     |      |  |
| tat        | ttt         | gaa         | ctt         | aaa        | gct        | aat | tta        | cat        | gct         | gaa | cct | gac | tat | tta | gaa | 3032 |  |
| Tyr        | Phe         | Glu         | Leu         | Lys        | Ala        | Asn | Leu        | His        | Ala         | Glu | Pro | Asp | Tyr | Leu | Glu |      |  |
|            |             |             | 820         |            |            | 825 |            |            |             | 830 |     |     |     |     | 835 |      |  |
| gtc        | ctg         | gag         | cag         | caa        | aca        | tag | atggagagtt | tgagggcttt | cgagagaaatg |     |     |     |     |     |     | 3083 |  |
| Val        | Leu         | Glu         | Gln         | Thr        | *          |     |            |            |             |     |     |     |     |     |     |      |  |
|            |             |             |             | 840        |            |     |            |            |             |     |     |     |     |     |     |      |  |
| ctgtgattct | gttttaagtc  | cataccttgt  | aaataagtgc  | cttacgtgag | tgtgtcatca |     |            |            |             |     |     |     |     |     |     | 3143 |  |
| atcagaacct | aagcacagca  | gtaaactatg  | gggaaaaaaaa | aagaagaaga | aaaagaaact |     |            |            |             |     |     |     |     |     |     | 3203 |  |
| cagggatcac | tgggagaagc  | catggcatta  | tcttcaggca  | atttagtctg | tcccaaataa |     |            |            |             |     |     |     |     |     |     | 3263 |  |
| aataaatcct | tgcattgtaa  | tcattcaagg  | attatagtaa  | tatttcatat | actgaaaagt |     |            |            |             |     |     |     |     |     |     | 3323 |  |
| gtctcatagg | agtcctcttg  | cacatctaaa  | aaggctgaac  | atttaagtat | cccgaatttt |     |            |            |             |     |     |     |     |     |     | 3383 |  |
| cttgaattgc | tttccctata  | gattaattac  | aattggattt  | catcatttaa | aaaccatact |     |            |            |             |     |     |     |     |     |     | 3443 |  |
| tgtatatgta | gttataatat  | gtaaggaata  | cattgtttat  | aaccagtatg | tacttcaaaa |     |            |            |             |     |     |     |     |     |     | 3503 |  |
| atgtgtattg | tcaaacatac  | ctaactttct  | tgcaataaat  | gcaaaagaaa | ctggaacttg |     |            |            |             |     |     |     |     |     |     | 3563 |  |
| acaattataa | atagtaatat  | tgaagaaaaa  | atagaaaggt  | tgcaattata | taggccatgg |     |            |            |             |     |     |     |     |     |     | 3623 |  |
| gtggctcaaa | actttgaaca  | tttgagctta  | aacaaatgcc  | actctcatgc | attctaaatt |     |            |            |             |     |     |     |     |     |     | 3683 |  |
| aaaaagttaa | aatgattaat  | agttcagggt  | gaagaaataa  | gcatactttt | tgggttttct |     |            |            |             |     |     |     |     |     |     | 3743 |  |
| acacattttg | tgtagacaat  | tttaattgtc  | gtgctgctgt  | gaactaaagt | atgtcattta |     |            |            |             |     |     |     |     |     |     | 3803 |  |
| tgctcaaagt | ttaattcttc  | ttcttgggat  | attttaaaaa  | tgctactgag | attctgctgt |     |            |            |             |     |     |     |     |     |     | 3863 |  |
| aaatatgact | agagaatata  | ttgggtttgc  | tttatttcat  | aggcttaatt | ctttgtaaat |     |            |            |             |     |     |     |     |     |     | 3923 |  |
| ctgaatgacc | ataatagaaa  | tacatttctt  | gtggcaagta  | attcacagtt | gtaaagtata |     |            |            |             |     |     |     |     |     |     | 3983 |  |
| taggaaaaat | tatttttatt  | ttattgatgt  | acattgatag  | atgccataaa | tcagtagcaa |     |            |            |             |     |     |     |     |     |     | 4043 |  |
| aaggcacttc | taaaggttaag | tgggtttaagt | tgctcaaga   | gagggacaat | gtagctttat |     |            |            |             |     |     |     |     |     |     | 4103 |  |
| tttacaagaa | ggcatagtta  | gatttctatg  | aaatatttat  | tctgtacagt | tttatatagt |     |            |            |             |     |     |     |     |     |     | 4163 |  |
| tttgggtcac | aaaagtaatt  | attcttgggt  | gcctttcaag  | aaaattaaaa | atactactca |     |            |            |             |     |     |     |     |     |     | 4223 |  |
| ctacaataaa | actaaaatga  | aaactcttt   |             |            |            |     |            |            |             |     |     |     |     |     |     | 4252 |  |

&lt;210&gt; SEQ ID NO 20

&lt;211&gt; LENGTH: 841

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 20

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Leu | Trp | Ile | His | Leu | Phe | Tyr | Ser | Ser | Leu | Leu | Ala | Cys | Ile |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | His | Ser | Gln | Thr | Pro | Val | Leu | Ser | Ser | Arg | Gly | Ser | Cys | Asp |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Cys | Asn | Cys | Glu | Glu | Lys | Asp | Gly | Thr | Met | Leu | Ile | Asn | Cys |
|     | 35  |     |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Glu | Ala | Lys | Gly | Ile | Lys | Met | Val | Ser | Glu | Ile | Ser | Val | Pro | Pro | Ser |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Arg | Pro | Phe | Gln | Leu | Ser | Leu | Leu | Asn | Asn | Gly | Leu | Thr | Met | Leu | His |
|     | 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Thr | Asn | Asp | Phe | Ser | Gly | Leu | Thr | Asn | Ala | Ile | Ser | Ile | His | Leu | Gly |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Phe | Asn | Asn | Ile | Ala | Asp | Ile | Glu | Ile | Gly | Ala | Phe | Asn | Gly | Leu | Gly |
|     |     |     | 100 |     |     |     |     |     | 105 |     |     |     | 110 |     |     |
| Leu | Leu | Lys | Gln | Leu | His | Ile | Asn | His | Asn | Ser | Leu | Glu | Ile | Leu | Lys |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Glu | Asp | Thr | Phe | His | Gly | Leu | Glu | Asn | Leu | Glu | Phe | Leu | Gln | Ala | Asp |
|     | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |
| Asn | Asn | Phe | Ile | Thr | Val | Ile | Glu | Pro | Ser | Ala | Phe | Ser | Lys | Leu | Asn |
|     | 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Arg | Leu | Lys | Val | Leu | Ile | Leu | Asn | Asp | Asn | Ala | Ile | Glu | Ser | Leu | Pro |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Pro | Asn | Ile | Phe | Arg | Phe | Val | Pro | Leu | Thr | His | Leu | Asp | Leu | Arg | Gly |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Asn | Gln | Leu | Gln | Thr | Leu | Pro | Tyr | Val | Gly | Phe | Leu | Glu | His | Ile | Gly |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Arg | Ile | Leu | Asp | Leu | Gln | Leu | Glu | Asp | Asn | Lys | Trp | Ala | Cys | Asn | Cys |
|     | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |
| Asp | Leu | Leu | Gln | Leu | Lys | Thr | Trp | Leu | Glu | Asn | Met | Pro | Pro | Gln | Ser |
|     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Ile | Ile | Gly | Asp | Val | Val | Cys | Asn | Ser | Pro | Phe | Phe | Lys | Gly | Ser |     |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     | 255 |     |     |
| Ile | Leu | Ser | Arg | Leu | Lys | Lys | Glu | Ser | Ile | Cys | Pro | Thr | Pro | Pro | Val |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Tyr | Glu | Glu | His | Glu | Asp | Pro | Ser | Gly | Ser | Leu | His | Leu | Ala | Ala | Thr |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Ser | Ser | Ile | Asn | Asp | Ser | Arg | Met | Ser | Thr | Lys | Thr | Thr | Ser | Ile | Leu |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Lys | Leu | Pro | Thr | Lys | Ala | Pro | Gly | Leu | Ile | Pro | Tyr | Ile | Thr | Lys | Pro |
|     | 305 |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Ser | Thr | Gln | Leu | Pro | Gly | Pro | Tyr | Cys | Pro | Ile | Pro | Cys | Asn | Cys | Lys |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     | 335 |     |     |
| Val | Leu | Ser | Pro | Ser | Gly | Leu | Leu | Ile | His | Cys | Gln | Glu | Arg | Asn | Ile |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Glu | Ser | Leu | Ser | Asp | Leu | Arg | Pro | Pro | Gln | Asn | Pro | Arg | Lys | Leu |     |
|     |     | 355 |     |     |     | 360 |     |     |     |     | 365 |     |     |     |     |
| Ile | Leu | Ala | Gly | Asn | Ile | Ile | His | Ser | Leu | Met | Lys | Ser | Asp | Leu | Val |
|     |     | 370 |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Glu | Tyr | Phe | Thr | Leu | Glu | Met | Leu | His | Leu | Gly | Asn | Asn | Arg | Ile | Glu |
|     | 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Val | Leu | Glu | Glu | Gly | Ser | Phe | Met | Asn | Leu | Thr | Arg | Leu | Gln | Lys | Leu |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Tyr | Leu | Asn | Gly | Asn | His | Leu | Thr | Lys | Leu | Ser | Lys | Gly | Met | Phe | Leu |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Leu | His | Asn | Leu | Glu | Tyr | Leu | Tyr | Leu | Glu | Tyr | Asn | Ala | Ile | Lys |
| 435 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Glu | Ile | Leu | Pro | Gly | Thr | Phe | Asn | Pro | Met | Pro | Lys | Leu | Lys | Val | Leu |
| 450 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Tyr | Leu | Asn | Asn | Asn | Leu | Leu | Gln | Val | Leu | Pro | Pro | His | Ile | Phe | Ser |
| 465 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Gly | Val | Pro | Leu | Thr | Lys | Val | Asn | Leu | Lys | Thr | Asn | Gln | Phe | Thr | His |
| 485 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Leu | Pro | Val | Ser | Asn | Ile | Leu | Asp | Asp | Leu | Asp | Leu | Leu | Thr | Gln | Ile |
| 500 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Asp | Leu | Glu | Asp | Asn | Pro | Trp | Asp | Cys | Ser | Cys | Asp | Leu | Val | Gly | Leu |
| 515 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Gln | Gln | Trp | Ile | Gln | Lys | Leu | Ser | Lys | Asn | Thr | Val | Thr | Asp | Asp | Ile |
| 530 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Leu | Cys | Thr | Ser | Pro | Gly | His | Leu | Asp | Lys | Lys | Glu | Leu | Lys | Ala | Leu |
| 545 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Asn | Ser | Glu | Ile | Leu | Cys | Pro | Gly | Leu | Val | Asn | Asn | Pro | Ser | Met | Pro |
| 565 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Thr | Gln | Thr | Ser | Tyr | Leu | Met | Val | Thr | Thr | Pro | Ala | Thr | Thr | Thr | Asn |
| 580 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Thr | Ala | Asp | Thr | Ile | Leu | Arg | Ser | Leu | Thr | Asp | Ala | Val | Pro | Leu | Ser |
| 595 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Val | Leu | Ile | Leu | Gly | Leu | Leu | Ile | Met | Phe | Ile | Thr | Ile | Val | Phe | Cys |
| 610 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Ala | Ala | Gly | Ile | Val | Val | Leu | Val | Leu | His | Arg | Arg | Arg | Arg | Tyr | Lys |
| 625 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Lys | Lys | Gln | Val | Asp | Glu | Gln | Met | Arg | Asp | Asn | Ser | Pro | Val | His | Leu |
| 645 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Gln | Tyr | Ser | Met | Tyr | Gly | His | Lys | Thr | Thr | His | His | Thr | Thr | Glu | Arg |
| 660 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Pro | Ser | Ala | Ser | Leu | Tyr | Glu | Gln | His | Met | Val | Ser | Pro | Met | Val | His |
| 675 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Val | Tyr | Arg | Ser | Pro | Ser | Phe | Gly | Pro | Lys | His | Leu | Glu | Glu | Glu | Glu |
| 690 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Glu | Arg | Asn | Glu | Lys | Glu | Gly | Ser | Asp | Ala | Lys | His | Leu | Gln | Arg | Ser |
| 705 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Leu | Leu | Glu | Gln | Glu | Asn | His | Ser | Pro | Leu | Thr | Gly | Ser | Asn | Met | Lys |
| 725 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Tyr | Lys | Thr | Thr | Asn | Gln | Ser | Thr | Glu | Phe | Leu | Ser | Phe | Gln | Asp | Ala |
| 740 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Ser | Ser | Leu | Tyr | Arg | Asn | Ile | Leu | Glu | Lys | Glu | Arg | Glu | Leu | Gln | Gln |
| 755 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Leu | Gly | Ile | Thr | Glu | Tyr | Leu | Arg | Lys | Asn | Ile | Ala | Gln | Leu | Gln | Pro |
| 770 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Asp | Met | Glu | Ala | His | Tyr | Pro | Gly | Ala | His | Glu | Glu | Leu | Lys | Leu | Met |
| 785 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Glu | Thr | Leu | Met | Tyr | Ser | Arg | Pro | Arg | Lys | Val | Leu | Val | Glu | Gln | Thr |
| 805 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Lys | Asn | Glu | Tyr | Phe | Glu | Leu | Lys | Ala | Asn | Leu | His | Ala | Glu | Pro | Asp |
| 820 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Tyr | Leu | Glu | Val | Leu | Glu | Gln | Gln | Thr |     |     |     |     |     |     |     |

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| 835                                                               | 840 |                     |
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| <210> SEQ ID NO 21                                                |     |                     |
| <211> LENGTH: 3609                                                |     |                     |
| <212> TYPE: DNA                                                   |     |                     |
| <213> ORGANISM: human                                             |     |                     |
| <220> FEATURE:                                                    |     |                     |
| <221> NAME/KEY: CDS                                               |     |                     |
| <222> LOCATION: (282) ... (2549)                                  |     |                     |
| <400> SEQUENCE: 21                                                |     |                     |
| cgaagggggc ggtggttccc cgcggcgctg cgcgcggcgg taattagtga ttgtcttcca | 60  |                     |
| gcttcgcgaa ggctaggggc gcggtgccc ggtggctgcg cggcgctgcc ccgggaccga  | 120 |                     |
| ggggcagcca atccaatgaa accacgcgct gttcgcgcct ggtagagatt tctcgaagac | 180 |                     |
| accagtgggc ccgttccgag ccctctggac cgcccgtgtg gaaccaaacc tgcgcgcgtg | 240 |                     |
| gccggggcgt gggacaacga ggccgcggag acgaaggcgc a atg gcg agg aag tta | 296 |                     |
|                                                                   |     | Met Ala Arg Lys Leu |
|                                                                   |     | 1 5                 |
| tct gta atc ttg atc ctg acc ttt gcc ctc tct gtc aca aat ccc ctt   | 344 |                     |
| Ser Val Ile Leu Ile Leu Thr Phe Ala Leu Ser Val Thr Asn Pro Leu   |     |                     |
|                                                                   |     | 10 15 20            |
| cat gaa cta aaa gca gct gct ttc ccc cag acc act gag aaa att agt   | 392 |                     |
| His Glu Leu Lys Ala Ala Ala Phe Pro Gln Thr Thr Glu Lys Ile Ser   |     |                     |
|                                                                   |     | 25 30 35            |
| ccg aat tgg gaa tct ggc att aat gtt gac ttg gca att tcc aca cgg   | 440 |                     |
| Pro Asn Trp Glu Ser Gly Ile Asn Val Asp Leu Ala Ile Ser Thr Arg   |     |                     |
|                                                                   |     | 40 45 50            |
| caa tat cat cta caa cag ctt ttc tac cgc tat gga gaa aat aat tct   | 488 |                     |
| Gln Tyr His Leu Gln Gln Leu Phe Tyr Arg Tyr Gly Glu Asn Asn Ser   |     |                     |
|                                                                   |     | 55 60 65            |
| ttg tca gtt gaa ggg ttc aga aaa tta ctt caa aat ata ggc ata gat   | 536 |                     |
| Leu Ser Val Glu Gly Phe Arg Lys Leu Leu Gln Asn Ile Gly Ile Asp   |     |                     |
|                                                                   |     | 70 75 80 85         |
| aag att aaa aga atc cat ata cac cat gac cac gac cat cac tca gac   | 584 |                     |
| Lys Ile Lys Arg Ile His Ile His His Asp His Asp His His Ser Asp   |     |                     |
|                                                                   |     | 90 95 100           |
| cac gag cat cac tca gac cat gag cgt cac tca gac cat gag cat cac   | 632 |                     |
| His Glu His His Ser Asp His Glu Arg His Ser Asp His Glu His His   |     |                     |
|                                                                   |     | 105 110 115         |
| tca gac cac gag cat cac tct gac cat gat cat cac tct cac cat aat   | 680 |                     |
| Ser Asp His Glu His His Ser Asp His Asp His His Ser His His Asn   |     |                     |
|                                                                   |     | 120 125 130         |
| cat gct gct tct ggt aaa aat aag cga aaa gct ctt tgc cca gac cat   | 728 |                     |
| His Ala Ala Ser Gly Lys Asn Lys Arg Lys Ala Leu Cys Pro Asp His   |     |                     |
|                                                                   |     | 135 140 145         |
| gac tca gat agt tca ggt aaa gat cct aga aac agc cag ggg aaa gga   | 776 |                     |
| Asp Ser Asp Ser Ser Gly Lys Asp Pro Arg Asn Ser Gln Gly Lys Gly   |     |                     |
|                                                                   |     | 150 155 160 165     |
| gct cac cga cca gaa cat gcc agt ggt aga agg aat gtc aag gac agt   | 824 |                     |
| Ala His Arg Pro Glu His Ala Ser Gly Arg Arg Asn Val Lys Asp Ser   |     |                     |
|                                                                   |     | 170 175 180         |
| gtt agt gct agt gaa gtg acc tca act gtg tac aac act gtc tct gaa   | 872 |                     |
| Val Ser Ala Ser Glu Val Thr Ser Thr Val Tyr Asn Thr Val Ser Glu   |     |                     |
|                                                                   |     | 185 190 195         |
| gga act cac ttt cta gag aca ata gag act cca aga cct gga aaa ctc   | 920 |                     |
| Gly Thr His Phe Leu Glu Thr Ile Glu Thr Pro Arg Pro Gly Lys Leu   |     |                     |
|                                                                   |     | 200 205 210         |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| ttc ccc aaa gat gta agc agc tcc act cca ccc agt gtc aca tca aag | 968  |
| Phe Pro Lys Asp Val Ser Ser Ser Thr Pro Pro Ser Val Thr Ser Lys |      |
| 215 220 225                                                     |      |
| agc cgg gtg agc cgg ctg gct ggt agg aaa aca aat gaa tct gtg agt | 1016 |
| Ser Arg Val Ser Arg Leu Ala Gly Arg Lys Thr Asn Glu Ser Val Ser |      |
| 230 235 240 245                                                 |      |
| gag ccc cga aaa ggc ttt atg tat tcc aga aac aca aat gaa aat cct | 1064 |
| Glu Pro Arg Lys Gly Phe Met Tyr Ser Arg Asn Thr Asn Glu Asn Pro |      |
| 250 255 260                                                     |      |
| cag gag tgt ttc aat gca tca aag cta ctg aca tct cat ggc atg ggc | 1112 |
| Gln Glu Cys Phe Asn Ala Ser Lys Leu Leu Thr Ser His Gly Met Gly |      |
| 265 270 275                                                     |      |
| atc cag gtt ccg ctg aat gca aca gag ttc aac tat ctc tgt cca gcc | 1160 |
| Ile Gln Val Pro Leu Asn Ala Thr Glu Phe Asn Tyr Leu Cys Pro Ala |      |
| 280 285 290                                                     |      |
| atc atc aac caa att gat gct aga tct tgt ctg att cat aca agt gaa | 1208 |
| Ile Ile Asn Gln Ile Asp Ala Arg Ser Cys Leu Ile His Thr Ser Glu |      |
| 295 300 305                                                     |      |
| aag aag gct gaa atc cct cca aag acc tat tca tta caa ata gcc tgg | 1256 |
| Lys Lys Ala Glu Ile Pro Pro Lys Thr Tyr Ser Leu Gln Ile Ala Trp |      |
| 310 315 320 325                                                 |      |
| gtt ggt ggt ttt ata gcc att tcc atc atc agt ttc ctg tct ctg ctg | 1304 |
| Val Gly Gly Phe Ile Ala Ile Ser Ile Ile Ser Phe Leu Ser Leu Leu |      |
| 330 335 340                                                     |      |
| ggg gtt atc tta gtg cct ctc atg aat cgg gtg ttt ttc aaa ttt ctc | 1352 |
| Gly Val Ile Leu Val Pro Leu Met Asn Arg Val Phe Phe Lys Phe Leu |      |
| 345 350 355                                                     |      |
| ctg agt ttc ctt gtg gca ctg gcc gtt ggg act ttg agt ggt gat gct | 1400 |
| Leu Ser Phe Leu Val Ala Leu Ala Val Gly Thr Leu Ser Gly Asp Ala |      |
| 360 365 370                                                     |      |
| ttt tta cac ctt ctt cca cat tct cat gca agt cac cac cat agt cat | 1448 |
| Phe Leu His Leu Leu Pro His Ser His Ala Ser His His His Ser His |      |
| 375 380 385                                                     |      |
| agc cat gaa gaa cca gca atg gaa atg aaa aga gga cca ctt ttc agt | 1496 |
| Ser His Glu Glu Pro Ala Met Glu Met Lys Arg Gly Pro Leu Phe Ser |      |
| 390 395 400 405                                                 |      |
| cat ctg tct tct caa aac ata gaa gaa agt gcc tat ttt gat tcc acg | 1544 |
| His Leu Ser Ser Gln Asn Ile Glu Glu Ser Ala Tyr Phe Asp Ser Thr |      |
| 410 415 420                                                     |      |
| tgg aag ggt cta aca gct cta gga ggc ctg tat ttc atg ttt ctt gtt | 1592 |
| Trp Lys Gly Leu Thr Ala Leu Gly Gly Leu Tyr Phe Met Phe Leu Val |      |
| 425 430 435                                                     |      |
| gaa cat gtc ctc aca ttg atc aaa caa ttt aaa gat aag aag aaa aag | 1640 |
| Glu His Val Leu Thr Leu Ile Lys Gln Phe Lys Asp Lys Lys Lys Lys |      |
| 440 445 450                                                     |      |
| aat cag aag aaa cct gaa aat gat gat gat gtg gag att aag aag cag | 1688 |
| Asn Gln Lys Lys Pro Glu Asn Asp Asp Asp Val Glu Ile Lys Lys Gln |      |
| 455 460 465                                                     |      |
| ttg tcc aag tat gaa tct caa ctt tca aca aat gag gag aaa gta gat | 1736 |
| Leu Ser Lys Tyr Glu Ser Gln Leu Ser Thr Asn Glu Glu Lys Val Asp |      |
| 470 475 480 485                                                 |      |
| aca gat gat cga act gaa ggc tat tta cga gca gac tca caa gag ccc | 1784 |
| Thr Asp Asp Arg Thr Glu Gly Tyr Leu Arg Ala Asp Ser Gln Glu Pro |      |
| 490 495 500                                                     |      |
| tcc cac ttt gat tct cag cag cct gca gtc ttg gaa gaa gaa gag gtc | 1832 |
| Ser His Phe Asp Ser Gln Gln Pro Ala Val Leu Glu Glu Glu Glu Val |      |
| 505 510 515                                                     |      |

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|                                                                     |      |
|---------------------------------------------------------------------|------|
| atg ata gct cat gct cat cca cag gaa gtc tac aat gaa tat gta ccc     | 1880 |
| Met Ile Ala His Ala His Pro Gln Glu Val Tyr Asn Glu Tyr Val Pro     |      |
| 520 525 530                                                         |      |
| aga ggg tgc aag aat aaa tgc cat tca cat ttc cac gat aca ctc ggc     | 1928 |
| Arg Gly Cys Lys Asn Lys Cys His Ser His Phe His Asp Thr Leu Gly     |      |
| 535 540 545                                                         |      |
| cag tca gac gat ctc att cac cac cat cat gac tac cat cat att ctc     | 1976 |
| Gln Ser Asp Asp Leu Ile His His His His Asp Tyr His His Ile Leu     |      |
| 550 555 560 565                                                     |      |
| cat cat cac cac cac caa aac cac cat cct cac agt cac agc cag cgc     | 2024 |
| His His His His His Gln Asn His His Pro His Ser His Ser Gln Arg     |      |
| 570 575 580                                                         |      |
| tac tct cgg gag gag ctg aaa gat gcc ggc gtc gcc act ctg gcc tgg     | 2072 |
| Tyr Ser Arg Glu Glu Leu Lys Asp Ala Gly Val Ala Thr Leu Ala Trp     |      |
| 585 590 595                                                         |      |
| atg gtg ata atg ggt gat ggc ctg cac aat ttc agc gat ggc cta gca     | 2120 |
| Met Val Ile Met Gly Asp Gly Leu His Asn Phe Ser Asp Gly Leu Ala     |      |
| 600 605 610                                                         |      |
| att ggt gct gct ttt act gaa ggc tta tca agt ggt tta agt act tct     | 2168 |
| Ile Gly Ala Ala Phe Thr Glu Gly Leu Ser Ser Gly Leu Ser Thr Ser     |      |
| 615 620 625                                                         |      |
| gtt gct gtg ttc tgt cat gag ttg cct cat gaa tta ggt gac ttt gct     | 2216 |
| Val Ala Val Phe Cys His Glu Leu Pro His Glu Leu Gly Asp Phe Ala     |      |
| 630 635 640 645                                                     |      |
| gtt cta cta aag gct ggc atg acc gtt aag cag gct gtc ctt tat aat     | 2264 |
| Val Leu Leu Lys Ala Gly Met Thr Val Lys Gln Ala Val Leu Tyr Asn     |      |
| 650 655 660                                                         |      |
| gca ttg tca gcc atg ctg gcg tat ctt gga atg gca aca gga att ttc     | 2312 |
| Ala Leu Ser Ala Met Leu Ala Tyr Leu Gly Met Ala Thr Gly Ile Phe     |      |
| 665 670 675                                                         |      |
| att ggt cat tat gct gaa aat gtt tct atg tgg ata ttt gca ctt act     | 2360 |
| Ile Gly His Tyr Ala Glu Asn Val Ser Met Trp Ile Phe Ala Leu Thr     |      |
| 680 685 690                                                         |      |
| gct ggc tta ttc atg tat gtt gct ctg gtt gat atg gta cct gaa atg     | 2408 |
| Ala Gly Leu Phe Met Tyr Val Ala Leu Val Asp Met Val Pro Glu Met     |      |
| 695 700 705                                                         |      |
| ctg cac aat gat gct agt gac cat gga tgt agc cgc tgg ggg tat ttc     | 2456 |
| Leu His Asn Asp Ala Ser Asp His Gly Cys Ser Arg Trp Gly Tyr Phe     |      |
| 710 715 720 725                                                     |      |
| ttt tta cag aat gct ggg atg ctt ttg ggt ttt gga att atg tta ctt     | 2504 |
| Phe Leu Gln Asn Ala Gly Met Leu Leu Gly Phe Gly Ile Met Leu Leu     |      |
| 730 735 740                                                         |      |
| att tcc ata ttt gaa cat aaa atc gtg ttt cgt ata aat ttc tag         | 2549 |
| Ile Ser Ile Phe Glu His Lys Ile Val Phe Arg Ile Asn Phe *           |      |
| 745 750 755                                                         |      |
| ttaaggttta aatgctagag tagcttaaaa agttgtcata gtttcagtag gtcataggga   | 2609 |
| gatgagtttg tatgctgtac tatgcagcgt ttaaagtttag tgggttttgt gattttttat  | 2669 |
| tgaatattgc tgtctgttac aaagtcagtt aaaggtacgt tttaatatTTT aagttattct  | 2729 |
| atcttgagaga taaaatctgt atgtgcaatt caccggtatt accagtttat tatgtaacaa  | 2789 |
| agagattttgg catgacatgt tctgtatgtt tcagggaata atgtcttttaa tgctttttca | 2849 |
| agaactaaca cagttattcc tatactggat tttaggtctc tgaagaactg ctggtgttta   | 2909 |
| ggaataagaa tgtgcatgaa gcctaaaata ccaagaaagc ttatactgaa tttaagcaaa   | 2969 |
| gaaataaagg agaaaagaga agaactgtgag aattggggag gcatagattc ttataaaaat  | 3029 |

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cacaaaaattt gttgtaaatt agaggggaga aatttagaat taagtataaa aaggcagaat 3089
tagtatagag tacattcatt aaacattttt gtcaggatta tttcccgtaa aaacgtagtg 3149
agcacttttc atatactaatt ttagttgtac atttaacttt gtataataca gaaatctaaa 3209
tatatttaat gaattcaagc aatatatcac ttgaccaaga aattggaatt tcaaaatggt 3269
cgtgcgggta tataccagat gagtacagtg agtagtttta tgtatcacca gactgggtta 3329
ttgccaagtt atatatcacc aaaagctgta tgactggatg ttctgggttac ctgggtttaca 3389
aaattatcag agtagtaaaa ctttgatata tatgaggata ttaaaactac actaagtatc 3449
atttgattcg attcagaaag tactttgata tctctcagtg cttcagtgtc atcattgtga 3509
gcaattgtct tttatatacg gtactgtagc catactaggc ctgtctgtgg cattctctag 3569
atgtttcttt tttacacaat aaattcctta tatcagcttg 3609

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&lt;210&gt; SEQ ID NO 22

&lt;211&gt; LENGTH: 755

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 22

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Met Ala Arg Lys Leu Ser Val Ile Leu Ile Leu Thr Phe Ala Leu Ser
1           5           10          15
Val Thr Asn Pro Leu His Glu Leu Lys Ala Ala Ala Phe Pro Gln Thr
          20          25          30
Thr Glu Lys Ile Ser Pro Asn Trp Glu Ser Gly Ile Asn Val Asp Leu
          35          40          45
Ala Ile Ser Thr Arg Gln Tyr His Leu Gln Gln Leu Phe Tyr Arg Tyr
          50          55          60
Gly Glu Asn Asn Ser Leu Ser Val Glu Gly Phe Arg Lys Leu Leu Gln
65          70          75          80
Asn Ile Gly Ile Asp Lys Ile Lys Arg Ile His Ile His His Asp His
          85          90          95
Asp His His Ser Asp His Glu His His Ser Asp His Glu Arg His Ser
          100         105         110
Asp His Glu His His Ser Asp His Glu His His Ser Asp His Asp His
          115         120         125
His Ser His His Asn His Ala Ala Ser Gly Lys Asn Lys Arg Lys Ala
          130         135         140
Leu Cys Pro Asp His Asp Ser Asp Ser Ser Gly Lys Asp Pro Arg Asn
145         150         155         160
Ser Gln Gly Lys Gly Ala His Arg Pro Glu His Ala Ser Gly Arg Arg
          165         170         175
Asn Val Lys Asp Ser Val Ser Ala Ser Glu Val Thr Ser Thr Val Tyr
          180         185         190
Asn Thr Val Ser Glu Gly Thr His Phe Leu Glu Thr Ile Glu Thr Pro
          195         200         205
Arg Pro Gly Lys Leu Phe Pro Lys Asp Val Ser Ser Ser Thr Pro Pro
          210         215         220
Ser Val Thr Ser Lys Ser Arg Val Ser Arg Leu Ala Gly Arg Lys Thr
225         230         235         240
Asn Glu Ser Val Ser Glu Pro Arg Lys Gly Phe Met Tyr Ser Arg Asn
          245         250         255

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Asn | Glu | Asn | Pro | Gln | Glu | Cys | Phe | Asn | Ala | Ser | Lys | Leu | Leu | Thr |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ser | His | Gly | Met | Gly | Ile | Gln | Val | Pro | Leu | Asn | Ala | Thr | Glu | Phe | Asn |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Tyr | Leu | Cys | Pro | Ala | Ile | Ile | Asn | Gln | Ile | Asp | Ala | Arg | Ser | Cys | Leu |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ile | His | Thr | Ser | Glu | Lys | Lys | Ala | Glu | Ile | Pro | Pro | Lys | Thr | Tyr | Ser |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Leu | Gln | Ile | Ala | Trp | Val | Gly | Gly | Phe | Ile | Ala | Ile | Ser | Ile | Ile | Ser |
|     |     |     | 325 |     |     |     |     | 330 |     |     |     |     |     | 335 |     |
| Phe | Leu | Ser | Leu | Leu | Gly | Val | Ile | Leu | Val | Pro | Leu | Met | Asn | Arg | Val |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Phe | Phe | Lys | Phe | Leu | Leu | Ser | Phe | Leu | Val | Ala | Leu | Ala | Val | Gly | Thr |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Leu | Ser | Gly | Asp | Ala | Phe | Leu | His | Leu | Leu | Pro | His | Ser | His | Ala | Ser |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| His | His | His | Ser | His | Ser | His | Glu | Glu | Pro | Ala | Met | Glu | Met | Lys | Arg |
| 385 |     |     |     |     |     | 390 |     |     |     | 395 |     |     |     |     | 400 |
| Gly | Pro | Leu | Phe | Ser | His | Leu | Ser | Ser | Gln | Asn | Ile | Glu | Glu | Ser | Ala |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Tyr | Phe | Asp | Ser | Thr | Trp | Lys | Gly | Leu | Thr | Ala | Leu | Gly | Gly | Leu | Tyr |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Phe | Met | Phe | Leu | Val | Glu | His | Val | Leu | Thr | Leu | Ile | Lys | Gln | Phe | Lys |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Asp | Lys | Lys | Lys | Lys | Asn | Gln | Lys | Lys | Pro | Glu | Asn | Asp | Asp | Asp | Val |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Glu | Ile | Lys | Lys | Gln | Leu | Ser | Lys | Tyr | Glu | Ser | Gln | Leu | Ser | Thr | Asn |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Glu | Glu | Lys | Val | Asp | Thr | Asp | Asp | Arg | Thr | Glu | Gly | Tyr | Leu | Arg | Ala |
|     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |     | 495 |     |
| Asp | Ser | Gln | Glu | Pro | Ser | His | Phe | Asp | Ser | Gln | Gln | Pro | Ala | Val | Leu |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Glu | Glu | Glu | Glu | Val | Met | Ile | Ala | His | Ala | His | Pro | Gln | Glu | Val | Tyr |
|     | 515 |     |     |     |     | 520 |     |     |     |     |     | 525 |     |     |     |
| Asn | Glu | Tyr | Val | Pro | Arg | Gly | Cys | Lys | Asn | Lys | Cys | His | Ser | His | Phe |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| His | Asp | Thr | Leu | Gly | Gln | Ser | Asp | Asp | Leu | Ile | His | His | His | His | Asp |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Tyr | His | His | Ile | Leu | His | His | His | His | His | Gln | Asn | His | His | Pro | His |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Ser | His | Ser | Gln | Arg | Tyr | Ser | Arg | Glu | Glu | Leu | Lys | Asp | Ala | Gly | Val |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Ala | Thr | Leu | Ala | Trp | Met | Val | Ile | Met | Gly | Asp | Gly | Leu | His | Asn | Phe |
|     | 595 |     |     |     |     | 600 |     |     |     |     |     | 605 |     |     |     |
| Ser | Asp | Gly | Leu | Ala | Ile | Gly | Ala | Ala | Phe | Thr | Glu | Gly | Leu | Ser | Ser |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| Gly | Leu | Ser | Thr | Ser | Val | Ala | Val | Phe | Cys | His | Glu | Leu | Pro | His | Glu |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Leu | Gly | Asp | Phe | Ala | Val | Leu | Leu | Lys | Ala | Gly | Met | Thr | Val | Lys | Gln |
|     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     | 655 |     |

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Ala Val Leu Tyr Asn Ala Leu Ser Ala Met Leu Ala Tyr Leu Gly Met  
660 665 670

Ala Thr Gly Ile Phe Ile Gly His Tyr Ala Glu Asn Val Ser Met Trp  
675 680 685

Ile Phe Ala Leu Thr Ala Gly Leu Phe Met Tyr Val Ala Leu Val Asp  
690 695 700

Met Val Pro Glu Met Leu His Asn Asp Ala Ser Asp His Gly Cys Ser  
705 710 715 720

Arg Trp Gly Tyr Phe Phe Leu Gln Asn Ala Gly Met Leu Leu Gly Phe  
725 730 735

Gly Ile Met Leu Leu Ile Ser Ile Phe Glu His Lys Ile Val Phe Arg  
740 745 750

Ile Asn Phe  
755

<210> SEQ ID NO 23  
 <211> LENGTH: 2811  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (309) ... (1751)

<400> SEQUENCE: 23

cgaagggggc ggtggttccc cgcggcgctg cgcgcggcgg taattagtga ttgtcttcca 60

gcttcgcgaa ggctaggggc gcggctgccc ggtggctgcg cggcgctgcc cccggaccga 120

ggggcagcca atccaatgaa accaccgcgt gttcgcgcct ggtagagatt tctcgaagac 180

accagtgggc ccgttccgag ccctctggac cgcccgtgtg gaaccaaacc tgcgcgcgtg 240

gccgggccgt gggacaacga ggccgcggag actgtttcaa tgcataaaag ctactgacat 300

ctcatggc atg ggc atc cag gtt ccg ctg aat gca aca gag ttc aac tat 350  
 Met Gly Ile Gln Val Pro Leu Asn Ala Thr Glu Phe Asn Tyr  
 1 5 10

ctc tgt cca gcc atc atc aac caa att gat gct aga tct tgt ctg att 398  
 Leu Cys Pro Ala Ile Ile Asn Gln Ile Asp Ala Arg Ser Cys Leu Ile  
 15 20 25 30

cat aca agt gaa aag aag gct gaa atc cct cca aag acc tat tca tta 446  
 His Thr Ser Glu Lys Lys Ala Glu Ile Pro Pro Lys Thr Tyr Ser Leu  
 35 40 45

caa ata gcc tgg gtt ggt ggt ttt ata gcc att tcc atc atc agt ttc 494  
 Gln Ile Ala Trp Val Gly Gly Phe Ile Ala Ile Ser Ile Ile Ser Phe  
 50 55 60

ctg tct ctg ctg ggg gtt atc tta gtg cct ctc atg aat cgg gtg ttt 542  
 Leu Ser Leu Leu Gly Val Ile Leu Val Pro Leu Met Asn Arg Val Phe  
 65 70 75

ttc aaa ttt ctc ctg agt ttc ctt gtg gca ctg gcc gtt ggg act ttg 590  
 Phe Lys Phe Leu Leu Ser Phe Leu Val Ala Leu Ala Val Gly Thr Leu  
 80 85 90

agt ggt gat gct ttt tta cac ctt ctt cca cat tct cat gca agt cac 638  
 Ser Gly Asp Ala Phe Leu His Leu Leu Pro His Ser His Ala Ser His  
 95 100 105 110

cac cat agt cat agc cat gaa gaa cca gca atg gaa atg aaa aga gga 686  
 His His Ser His Ser His Glu Glu Pro Ala Met Glu Met Lys Arg Gly  
 115 120 125

cca ctt ttc agt cat ctg tct tct caa aac ata gaa gaa agt gcc tat 734  
 Pro Leu Phe Ser His Leu Ser Ser Gln Asn Ile Glu Glu Ser Ala Tyr

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| 130                                                                                                                                                   | 135 | 140 |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| ttt gat tcc acg tgg aag ggt cta aca gct cta gga ggc ctg tat ttc<br>Phe Asp Ser Thr Trp Lys Gly Leu Thr Ala Leu Gly Gly Leu Tyr Phe<br>145 150 155     |     |     | 782  |
| atg ttt ctt gtt gaa cat gtc ctc aca ttg atc aaa caa ttt aaa gat<br>Met Phe Leu Val Glu His Val Leu Thr Leu Ile Lys Gln Phe Lys Asp<br>160 165 170     |     |     | 830  |
| aag aag aaa aag aat cag aag aaa cct gaa aat gat gat gat gtg gag<br>Lys Lys Lys Lys Asn Gln Lys Lys Pro Glu Asn Asp Asp Val Glu<br>175 180 185 190     |     |     | 878  |
| att aag aag cag ttg tcc aag tat gaa tct caa ctt tca aca aat gag<br>Ile Lys Lys Gln Leu Ser Lys Tyr Glu Ser Gln Leu Ser Thr Asn Glu<br>195 200 205     |     |     | 926  |
| gag aaa gta gat aca gat gat cga act gaa ggc tat tta cga gca gac<br>Glu Lys Val Asp Thr Asp Asp Arg Thr Glu Gly Tyr Leu Arg Ala Asp<br>210 215 220     |     |     | 974  |
| tca caa gag ccc tcc cac ttt gat tct cag cag cct gca gtc ttg gaa<br>Ser Gln Glu Pro Ser His Phe Asp Ser Gln Gln Pro Ala Val Leu Glu<br>225 230 235     |     |     | 1022 |
| gaa gaa gag gtc atg ata gct cat gct cat cca cag gaa gtc tac aat<br>Glu Glu Glu Val Met Ile Ala His Ala His Pro Gln Glu Val Tyr Asn<br>240 245 250     |     |     | 1070 |
| gaa tat gta ccc aga ggg tgc aag aat aaa tgc cat tca cat ttc cac<br>Glu Tyr Val Pro Arg Gly Cys Lys Asn Lys Cys His Ser His Phe His<br>255 260 265 270 |     |     | 1118 |
| gat aca ctc ggc cag tca gac gat ctc att cac cac cat cat gac tac<br>Asp Thr Leu Gly Gln Ser Asp Asp Leu Ile His His His His Asp Tyr<br>275 280 285     |     |     | 1166 |
| cat cat att ctc cat cat cac cac cac caa aac cac cat cct cac agt<br>His His Ile Leu His His His His His Gln Asn His His Pro His Ser<br>290 295 300     |     |     | 1214 |
| cac agc cag cgc tac tct cgg gag gag ctg aaa gat gcc ggc gtc gcc<br>His Ser Gln Arg Tyr Ser Arg Glu Glu Leu Lys Asp Ala Gly Val Ala<br>305 310 315     |     |     | 1262 |
| act ctg gcc tgg atg gtg ata atg ggt gat ggc ctg cac aat ttc agc<br>Thr Leu Ala Trp Met Val Ile Met Gly Asp Gly Leu His Asn Phe Ser<br>320 325 330     |     |     | 1310 |
| gat ggc cta gca att ggt gct gct ttt act gaa ggc tta tca agt ggt<br>Asp Gly Leu Ala Ile Gly Ala Ala Phe Thr Glu Gly Leu Ser Ser Gly<br>335 340 345 350 |     |     | 1358 |
| tta agt act tct gtt gct gtg ttc tgt cat gag ttg cct cat gaa tta<br>Leu Ser Thr Ser Val Ala Val Phe Cys His Glu Leu Pro His Glu Leu<br>355 360 365     |     |     | 1406 |
| ggt gac ttt gct gtt cta cta aag gct ggc atg acc gtt aag cag gct<br>Gly Asp Phe Ala Val Leu Leu Lys Ala Gly Met Thr Val Lys Gln Ala<br>370 375 380     |     |     | 1454 |
| gtc ctt tat aat gca ttg tca gcc atg ctg gcg tat ctt gga atg gca<br>Val Leu Tyr Asn Ala Leu Ser Ala Met Leu Ala Tyr Leu Gly Met Ala<br>385 390 395     |     |     | 1502 |
| aca gga att ttc att ggt cat tat gct gaa aat gtt tct atg tgg ata<br>Thr Gly Ile Phe Ile Gly His Tyr Ala Glu Asn Val Ser Met Trp Ile<br>400 405 410     |     |     | 1550 |
| ttt gca ctt act gct ggc tta ttc atg tat gtt gct ctg gtt gat atg<br>Phe Ala Leu Thr Ala Gly Leu Phe Met Tyr Val Ala Leu Val Asp Met<br>415 420 425 430 |     |     | 1598 |
| gta cct gaa atg ctg cac aat gat gct agt gac cat gga tgt agc cgc<br>Val Pro Glu Met Leu His Asn Asp Ala Ser Asp His Gly Cys Ser Arg<br>440 445 450     |     |     | 1646 |

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| 435                                                                | 440 | 445 |      |
|--------------------------------------------------------------------|-----|-----|------|
| tgg ggg tat ttc ttt tta cag aat gct ggg atg ctt ttg ggt ttt gga    |     |     | 1694 |
| Trp Gly Tyr Phe Phe Leu Gln Asn Ala Gly Met Leu Leu Gly Phe Gly    |     |     |      |
| 450                                                                | 455 | 460 |      |
| att atg tta ctt att tcc ata ttt gaa cat aaa atc gtg ttt cgt ata    |     |     | 1742 |
| Ile Met Leu Leu Ile Ser Ile Phe Glu His Lys Ile Val Phe Arg Ile    |     |     |      |
| 465                                                                | 470 | 475 |      |
| aat ttc tag ttaagggttta aatgctagag tagcttaaaa agttgtcata           |     |     | 1791 |
| Asn Phe *                                                          |     |     |      |
| 480                                                                |     |     |      |
| gtttcagtag gtcataggga gatgagtttg tatgctgtac tatgcagcgt ttaaagttag  |     |     | 1851 |
| tgggttttgt gattttttat tgaatattgc tgtctgttac aaagtcagtt aaaggtagct  |     |     | 1911 |
| tttaatatatt aagttattct atcttggaga taaaatctgt atgtgcaatt caccggtatt |     |     | 1971 |
| accagtttat tatgtaaaca agagatttgg catgacatgt tctgtatggt tcagggaata  |     |     | 2031 |
| atgtctttaa tgctttttca agaactaaca cagttattcc tatactggat tttaggtctc  |     |     | 2091 |
| tgaagaactg ctggtgttta ggaataagaa tgtgcatgaa gcctaaaata ccaagaaagc  |     |     | 2151 |
| ttatactgaa ttaagcaaa gaaataaagg agaaaagaga agaactctgag aattggggag  |     |     | 2211 |
| gcatagattc ttataaaaat cacaaaattt gttgtaaatt agaggggaga aatttagaat  |     |     | 2271 |
| taagtataaa aaggcagaat tagtatagag tacattcatt aaacattttt gtcaggatta  |     |     | 2331 |
| tttcccgtaa aaacgtagtg agcacttttc atatactaat ttagttgtac atttaacttt  |     |     | 2391 |
| gtataatata gaaatctaaa tatatttaat gaattcaagc aatatatcac ttgaccaaga  |     |     | 2451 |
| aattggaatt tcaaaatggt cgtgcgggta tataccagat gagtacagtg agtagtttta  |     |     | 2511 |
| tgtatcacca gactgggtta ttgccaagtt atatatcacc aaaagctgta tgactggatg  |     |     | 2571 |
| ttctggttac ctggtttaca aaattatcag agtagtaaaa ctttgatata tatgaggata  |     |     | 2631 |
| ttaaaactac actaagtatc atttgattcg attcagaaag tactttgata tctctcagtg  |     |     | 2691 |
| cttcagtgtc atcattgtga gcaattgtct tttatatacg gtactgtagc catactaggc  |     |     | 2751 |
| ctgtctgtgg cattctctag atgtttcttt tttacacaat aaattcctta tatcagcttg  |     |     | 2811 |

&lt;210&gt; SEQ ID NO 24

&lt;211&gt; LENGTH: 480

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 24

|                                                                 |     |     |    |
|-----------------------------------------------------------------|-----|-----|----|
| Met Gly Ile Gln Val Pro Leu Asn Ala Thr Glu Phe Asn Tyr Leu Cys |     |     |    |
| 1                                                               | 5   | 10  | 15 |
| Pro Ala Ile Ile Asn Gln Ile Asp Ala Arg Ser Cys Leu Ile His Thr |     |     |    |
| 20                                                              | 25  | 30  |    |
| Ser Glu Lys Lys Ala Glu Ile Pro Pro Lys Thr Tyr Ser Leu Gln Ile |     |     |    |
| 35                                                              | 40  | 45  |    |
| Ala Trp Val Gly Gly Phe Ile Ala Ile Ser Ile Ile Ser Phe Leu Ser |     |     |    |
| 50                                                              | 55  | 60  |    |
| Leu Leu Gly Val Ile Leu Val Pro Leu Met Asn Arg Val Phe Phe Lys |     |     |    |
| 65                                                              | 70  | 75  | 80 |
| Phe Leu Leu Ser Phe Leu Val Ala Leu Ala Val Gly Thr Leu Ser Gly |     |     |    |
| 85                                                              | 90  | 95  |    |
| Asp Ala Phe Leu His Leu Leu Pro His Ser His Ala Ser His His His |     |     |    |
| 100                                                             | 105 | 110 |    |

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Ser His Ser His Glu Glu Pro Ala Met Glu Met Lys Arg Gly Pro Leu
 115                      120                      125

Phe Ser His Leu Ser Ser Gln Asn Ile Glu Glu Ser Ala Tyr Phe Asp
 130                      135                      140

Ser Thr Trp Lys Gly Leu Thr Ala Leu Gly Gly Leu Tyr Phe Met Phe
 145                      150                      155                      160

Leu Val Glu His Val Leu Thr Leu Ile Lys Gln Phe Lys Asp Lys Lys
      165                      170                      175

Lys Lys Asn Gln Lys Lys Pro Glu Asn Asp Asp Asp Val Glu Ile Lys
      180                      185                      190

Lys Gln Leu Ser Lys Tyr Glu Ser Gln Leu Ser Thr Asn Glu Glu Lys
      195                      200                      205

Val Asp Thr Asp Asp Arg Thr Glu Gly Tyr Leu Arg Ala Asp Ser Gln
      210                      215                      220

Glu Pro Ser His Phe Asp Ser Gln Gln Pro Ala Val Leu Glu Glu Glu
 225                      230                      235                      240

Glu Val Met Ile Ala His Ala His Pro Gln Glu Val Tyr Asn Glu Tyr
      245                      250                      255

Val Pro Arg Gly Cys Lys Asn Lys Cys His Ser His Phe His Asp Thr
      260                      265                      270

Leu Gly Gln Ser Asp Asp Leu Ile His His His His Asp Tyr His His
      275                      280                      285

Ile Leu His His His His His Gln Asn His His Pro His Ser His Ser
      290                      295                      300

Gln Arg Tyr Ser Arg Glu Glu Leu Lys Asp Ala Gly Val Ala Thr Leu
 305                      310                      315                      320

Ala Trp Met Val Ile Met Gly Asp Gly Leu His Asn Phe Ser Asp Gly
      325                      330                      335

Leu Ala Ile Gly Ala Ala Phe Thr Glu Gly Leu Ser Ser Gly Leu Ser
      340                      345                      350

Thr Ser Val Ala Val Phe Cys His Glu Leu Pro His Glu Leu Gly Asp
      355                      360                      365

Phe Ala Val Leu Leu Lys Ala Gly Met Thr Val Lys Gln Ala Val Leu
      370                      375                      380

Tyr Asn Ala Leu Ser Ala Met Leu Ala Tyr Leu Gly Met Ala Thr Gly
 385                      390                      395                      400

Ile Phe Ile Gly His Tyr Ala Glu Asn Val Ser Met Trp Ile Phe Ala
      405                      410                      415

Leu Thr Ala Gly Leu Phe Met Tyr Val Ala Leu Val Asp Met Val Pro
      420                      425                      430

Glu Met Leu His Asn Asp Ala Ser Asp His Gly Cys Ser Arg Trp Gly
      435                      440                      445

Tyr Phe Phe Leu Gln Asn Ala Gly Met Leu Leu Gly Phe Gly Ile Met
      450                      455                      460

Leu Leu Ile Ser Ile Phe Glu His Lys Ile Val Phe Arg Ile Asn Phe
 465                      470                      475                      480

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<210> SEQ ID NO 25
<211> LENGTH: 2260
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:

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<400> SEQUENCE: 25

|            |            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| aagccacgca | gccccggggc | gg  | atg | gct | cca | gca | gca | tgg | cta | cga | agt | gca |     | 52  |     |
|            |            | 1   | Met | Ala | Pro | Ala | Ala | Trp | Leu | Arg | Ser | Ala |     |     |     |
|            |            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| gct        | gct        | cga | gca | cta | cta | cca | cct | atg | ctg | ctg | ctg | ctc | cag | ccg | 100 |
| Ala        | Ala        | Arg | Ala | Leu | Leu | Pro | Pro | Met | Leu | Leu | Leu | Leu | Leu | Pro |     |
|            |            |     |     | 15  |     |     |     |     | 20  |     |     |     | 25  |     |     |
| ccg        | ccg        | ctg | ctg | gcc | cgg | gct | ctg | ccg | ccg | gac | gtc | cac | cac | ctc | 148 |
| Pro        | Pro        | Leu | Leu | Ala | Arg | Ala | Leu | Pro | Pro | Asp | Val | His | His | Leu |     |
|            |            |     |     | 30  |     |     |     | 35  |     |     |     |     | 40  |     |     |
| gcc        | gag        | agg | agg | ggg | cca | cag | ccc | tgg | cat | gca | gcc | ctg | ccc | agt | 196 |
| Ala        | Glu        | Arg | Arg | Gly | Pro | Gln | Pro | Trp | His | Ala | Ala | Leu | Pro | Ser |     |
|            |            |     |     | 45  |     |     | 50  |     |     |     |     | 55  |     | Ser |     |
| ccg        | gca        | cct | gcc | cct | gcc | acg | cag | gaa | gcc | ccc | cgg | cct | gcc | agc | 244 |
| Pro        | Ala        | Pro | Ala | Pro | Ala | Thr | Gln | Glu | Ala | Pro | Arg | Pro | Ala | Ser |     |
|            |            |     |     |     |     | 65  |     |     |     |     | 70  |     |     | Ser |     |
| ctc        | agg        | cct | ccc | cgc | tgt | ggc | gtg | ccc | gac | cca | tct | gat | ggg | ctg | 292 |
| Leu        | Arg        | Pro | Pro | Arg | Cys | Gly | Val | Pro | Asp | Pro | Ser | Asp | Gly | Leu |     |
|            |            |     |     |     | 80  |     |     |     |     | 85  |     |     |     | Ser |     |
| gcc        | cgc        | aac | cga | cag | aag | agg | ttc | gtg | ctt | tct | ggc | ggg | cgc | tgg | 340 |
| Ala        | Arg        | Asn | Arg | Gln | Lys | Arg | Phe | Val | Leu | Ser | Gly | Gly | Arg | Trp |     |
|            |            |     |     | 95  |     |     | 100 |     |     |     |     |     |     | Glu |     |
| aag        | acg        | gac | ctc | acc | tac | agg | atc | ctt | cgg | ttc | cca | tgg | cag | ttg | 388 |
| Lys        | Thr        | Asp | Leu | Thr | Tyr | Arg | Ile | Leu | Arg | Phe | Pro | Trp | Gln | Leu |     |
|            |            |     |     | 110 |     |     | 115 |     |     |     |     |     | 120 | Val |     |
| cag        | gag        | cag | gtg | cgg | cag | acg | atg | gca | gag | gcc | cta | aag | gta | tgg | 436 |
| Gln        | Glu        | Gln | Val | Arg | Gln | Thr | Met | Ala | Glu | Ala | Leu | Lys | Val | Trp |     |
|            |            |     |     | 125 |     |     | 130 |     |     |     |     | 135 |     | Ser |     |
| gat        | gtg        | acg | cca | ctc | acc | ttt | act | gag | gtg | cac | gag | ggc | cgt | gct | 484 |
| Asp        | Val        | Thr | Pro | Leu | Thr | Phe | Thr | Glu | Val | His | Glu | Gly | Arg | Ala |     |
|            |            |     |     |     |     | 145 |     |     |     |     | 150 |     |     | Asp |     |
| atc        | atg        | atc | gac | ttc | gcc | agg | tac | tgg | cat | ggg | gac | gac | ctg | ccg | 532 |
| Ile        | Met        | Ile | Asp | Phe | Ala | Arg | Tyr | Trp | His | Gly | Asp | Asp | Leu | Pro |     |
|            |            |     |     |     | 160 |     |     |     |     | 165 |     |     |     | Phe |     |
| gat        | ggg        | cct | ggg | ggc | atc | ctg | gcc | cat | gcc | ttc | ttc | ccc | aag | act | 580 |
| Asp        | Gly        | Pro | Gly | Gly | Ile | Leu | Ala | His | Ala | Phe | Phe | Pro | Lys | Thr |     |
|            |            |     |     | 175 |     |     | 180 |     |     |     |     |     |     | His |     |
| cga        | gaa        | ggg | gat | gtc | cac | ttc | gac | tat | gat | gag | acc | tgg | act | atc | 628 |
| Arg        | Glu        | Gly | Asp | Val | His | Phe | Asp | Tyr | Asp | Glu | Thr | Trp | Thr | Ile |     |
|            |            |     |     | 190 |     |     | 195 |     |     |     |     |     | 200 | Gly |     |
| gat        | gac        | cag | ggc | aca | gac | ctg | ctg | cag | gtg | gca | gcc | cat | gaa | ttt | 676 |
| Asp        | Asp        | Gln | Gly | Thr | Asp | Leu | Leu | Gln | Val | Ala | Ala | His | Glu | Phe |     |
|            |            |     |     | 205 |     |     | 210 |     |     |     |     | 215 |     | Gly |     |
| cac        | gtg        | ctg | ggg | ctg | cag |     |     |     |     |     |     |     |     |     |     |

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| gca ccg ctg gag cca gac gcc ccg cca gat gcc tgt gag gcc tcc ttt<br>Ala Pro Leu Glu Pro Asp Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe<br>285 290 295     | 916  |
| gac gcg gtc tcc acc atc cga ggc gag ctc ttt ttc ttc aaa gcg ggc<br>Asp Ala Val Ser Thr Ile Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly<br>300 305 310     | 964  |
| ttt gtg tgg cgc ctc cgt ggg ggc cag ctg cag ccc ggc tac cca gca<br>Phe Val Trp Arg Leu Arg Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala<br>315 320 325 330 | 1012 |
| ttg gcc tct cgc cac tgg cag gga ctg ccc agc cct gtg gac gct gcc<br>Leu Ala Ser Arg His Trp Gln Gly Leu Pro Ser Pro Val Asp Ala Ala<br>335 340 345     | 1060 |
| ttc gag gat gcc cag ggc cac att tgg ttc ttc caa ggt gct cag tac<br>Phe Glu Asp Ala Gln Gly His Ile Trp Phe Phe Gln Gly Ala Gln Tyr<br>350 355 360     | 1108 |
| tgg gtg tac gac ggt gaa aag cca gtc ctg ggc ccc gca ccc ctc acc<br>Trp Val Tyr Asp Gly Glu Lys Pro Val Leu Gly Pro Ala Pro Leu Thr<br>365 370 375     | 1156 |
| gag ctg ggc ctg gtg agg ttc ccg gtc cat gct gcc ttg gtc tgg ggt<br>Glu Leu Gly Leu Val Arg Phe Pro Val His Ala Ala Leu Val Trp Gly<br>380 385 390     | 1204 |
| ccc gag aag aac aag atc tac ttc ttc cga ggc agg gac tac tgg cgt<br>Pro Glu Lys Asn Lys Ile Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg<br>395 400 405 410 | 1252 |
| ttc cac ccc agc acc cgg cgt gta gac agt ccc gtg ccc cgc agg gcc<br>Phe His Pro Ser Thr Arg Arg Val Asp Ser Pro Val Pro Arg Arg Ala<br>415 420 425     | 1300 |
| act gac tgg aga ggg gtg ccc tct gag atc gac gct gcc ttc cag gat<br>Thr Asp Trp Arg Gly Val Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp<br>430 435 440     | 1348 |
| gct gat ggc tat gcc tac ttc ctg cgc ggc cgc ctc tac tgg aag ttt<br>Ala Asp Gly Tyr Ala Tyr Phe Leu Arg Gly Arg Leu Tyr Trp Lys Phe<br>445 450 455     | 1396 |
| gac cct gtg aag gtg aag gct ctg gaa ggc ttc ccc cgt ctc gtg ggt<br>Asp Pro Val Lys Val Lys Ala Leu Glu Gly Phe Pro Arg Leu Val Gly<br>460 465 470     | 1444 |
| cct gac ttc ttt ggc tgt gcc gag cct gcc aac act ttc ctc tga<br>Pro Asp Phe Phe Gly Cys Ala Glu Pro Ala Asn Thr Phe Leu *<br>475 480 485               | 1489 |
| ccatggcttg gatgcctca ggggtgctga cccctgccag gccacgaata tcaggctaga                                                                                      | 1549 |
| gaccocatggc catctttgtg gctgtgggca ccaggcatgg gactgagccc atgtctcttg                                                                                    | 1609 |
| caggggggatg ggggtgggta caaccacat gacaactgcc gggagggcca cgcaggctgt                                                                                     | 1669 |
| ggtcacctgc cagcgactgt ctcagactgg gcagggaggc tttggcatga cttaagagga                                                                                     | 1729 |
| agggcagtct tgggaccgc tatgcaggtc ctggcaaac tggtgcct gtctcatccc                                                                                         | 1789 |
| tgctcctcag ggtagacca tggcaggact gggggaactg gagtgtcctt gctgtatccc                                                                                      | 1849 |
| tggtgtgagg ttccttcag gggctggcac tgaagcaagg gtgctggggc cccatggcct                                                                                      | 1909 |
| tcagccctgg ctgagcaact gggctgtagg gcagggccac ttctgaggt caggtcttg                                                                                       | 1969 |
| taggtgctg catctgtctg ccttctggct gacaatcctg gaaatctgtt ctccagaatc                                                                                      | 2029 |
| caggccaaaa agttcacagt caaatgggga ggggtattct tcatgcagga gacccaggc                                                                                      | 2089 |
| cctggaggct gcaacatacc tcaatcctgt cccaggccgg atcctcctga agcccttttc                                                                                     | 2149 |
| gcagcactgc tatctccaa agccattgta aatgtgtgta cagtgtgtat aaaccttctt                                                                                      | 2209 |

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cttttttttt ttttttaaac tgaggattgt cattaaacac agttgttttc t

2260

&lt;210&gt; SEQ ID NO 26

&lt;211&gt; LENGTH: 488

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 26

Met Ala Pro Ala Ala Trp Leu Arg Ser Ala Ala Ala Arg Ala Leu Leu  
1 5 10 15

Pro Pro Met Leu Leu Leu Leu Gln Pro Pro Pro Leu Leu Ala Arg  
20 25 30

Ala Leu Pro Pro Asp Val His His Leu His Ala Glu Arg Arg Gly Pro  
35 40 45

Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala  
50 55 60

Thr Gln Glu Ala Pro Arg Pro Ala Ser Ser Leu Arg Pro Pro Arg Cys  
65 70 75 80

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

Arg Phe Val Leu Ser Gly Gly Arg Trp Glu Lys Thr Asp Leu Thr Tyr  
100 105 110

Arg Ile Leu Arg Phe Pro Trp Gln Leu Val Gln Glu Gln Val Arg Gln  
115 120 125

Thr Met Ala Glu Ala Leu Lys Val Trp Ser Asp Val Thr Pro Leu Thr  
130 135 140

Phe Thr Glu Val His Glu Gly Arg Ala Asp Ile Met Ile Asp Phe Ala  
145 150 155 160

Arg Tyr Trp His Gly Asp Asp Leu Pro Phe Asp Gly Pro Gly Gly Ile  
165 170 175

Leu Ala His Ala Phe Phe Pro Lys Thr His Arg Glu Gly Asp Val His  
180 185 190

Phe Asp Tyr Asp Glu Thr Trp Thr Ile Gly Asp Asp Gln Gly Thr Asp  
195 200 205

Leu Leu Gln Val Ala Ala His Glu Phe Gly His Val Leu Gly Leu Gln  
210 215 220

His Thr Thr Ala Ala Lys Ala Leu Met Ser Ala Phe Tyr Thr Phe Arg  
225 230 235 240

Tyr Pro Leu Ser Leu Ser Pro Asp Asp Cys Arg Gly Val Gln His Leu  
245 250 255

Tyr Gly Gln Pro Trp Pro Thr Val Thr Ser Arg Thr Pro Ala Leu Gly  
260 265 270

Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp  
275 280 285

Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile  
290 295 300

Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg  
305 310 315 320

Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp  
325 330 335

Gln Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly  
340 345 350

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His Ile Trp Phe Phe Gln Gly Ala Gln Tyr Trp Val Tyr Asp Gly Glu  
 355 360 365  
 Lys Pro Val Leu Gly Pro Ala Pro Leu Thr Glu Leu Gly Leu Val Arg  
 370 375 380  
 Phe Pro Val His Ala Ala Leu Val Trp Gly Pro Glu Lys Asn Lys Ile  
 385 390 395 400  
 Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg  
 405 410 415  
 Arg Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val  
 420 425 430  
 Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr  
 435 440 445  
 Phe Leu Arg Gly Arg Leu Tyr Trp Lys Phe Asp Pro Val Lys Val Lys  
 450 455 460  
 Ala Leu Glu Gly Phe Pro Arg Leu Val Gly Pro Asp Phe Phe Gly Cys  
 465 470 475 480  
 Ala Glu Pro Ala Asn Thr Phe Leu  
 485

<210> SEQ ID NO 27  
 <211> LENGTH: 2778  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (272) ... (1426)

<400> SEQUENCE: 27

agcggaaatct ttaggatctg agcaggagaa ataccagcgg atcttcccca ctctgctccc 60  
 ttccattccc acccttcctt ctttaataag caggagcgaa aaagacaaat tccaaagagg 120  
 attgttcagt tcaagggaat gaagaattca gaataatttt ggtaaatgga ttccaatatg 180  
 gggaataaga ataagctgaa cagttgacct gctttgaaga aacatactgt ccatttgtct 240  
 aaaataatct ataacaacca aaccaatcaa a atg aat tca aca tta ttt tcc 292  
 Met Asn Ser Thr Leu Phe Ser  
 1 5  
 cag gtt gaa aat cat tca gtc cac tct aat ttc tca gag aag aat gcc 340  
 Gln Val Glu Asn His Ser Val His Ser Asn Phe Ser Glu Lys Asn Ala  
 10 15 20  
 cag ctt ctg gct ttt gaa aat gat gat tgt cat ctg ccc ttg gcc atg 388  
 Gln Leu Leu Ala Phe Glu Asn Asp Asp Cys His Leu Pro Leu Ala Met  
 25 30 35  
 ata ttt acc tta gct ctt gct tat gga gct gtg atc att ctt ggt gtc 436  
 Ile Phe Thr Leu Ala Leu Ala Tyr Gly Ala Val Ile Ile Leu Gly Val  
 40 45 50 55  
 tct gga aac ctg gcc ttg atc ata atc atc ttg aaa caa aag gag atg 484  
 Ser Gly Asn Leu Ala Leu Ile Ile Ile Ile Leu Lys Gln Lys Glu Met  
 60 65 70  
 aga aat gtt acc aac atc ctg att gtg aac ctt tcc ttc tca gac ttg 532  
 Arg Asn Val Thr Asn Ile Leu Ile Val Asn Leu Ser Phe Ser Asp Leu  
 75 80 85  
 ctt gtt gcc atc atg tgt ctc ccc ttt aca ttt gtc tac aca tta atg 580  
 Leu Val Ala Ile Met Cys Leu Pro Phe Thr Phe Val Tyr Thr Leu Met  
 90 95 100  
 gac cac tgg gtc ttt ggt gag gcg atg tgt aag ttg aat cct ttt gtg 628

|            |             |            |            |            |             |     |     |     |     |            |            |     |     |     |     |      |
|------------|-------------|------------|------------|------------|-------------|-----|-----|-----|-----|------------|------------|-----|-----|-----|-----|------|
| Asp        | His         | Trp        | Val        | Phe        | Gly         | Glu | Ala | Met | Cys | Lys        | Leu        | Asn | Pro | Phe | Val |      |
| 105        |             |            |            |            |             | 110 |     |     |     |            | 115        |     |     |     |     |      |
| caa        | tgt         | gtt        | tca        | atc        | act         | gtg | tcc | att | ttc | tct        | ctg        | gtt | ctc | att | gct | 676  |
| Gln        | Cys         | Val        | Ser        | Ile        | Thr         | Val | Ser | Ile | Phe | Ser        | Leu        | Val | Leu | Ile | Ala |      |
| 120        |             |            |            |            |             | 125 |     |     |     | 130        |            |     |     |     | 135 |      |
| gtg        | gaa         | cga        | cat        | cag        | ctg         | ata | atc | aac | cct | cga        | ggg        | tgg | aga | cca | aat | 724  |
| Val        | Glu         | Arg        | His        | Gln        | Leu         | Ile | Ile | Asn | Pro | Arg        | Gly        | Trp | Arg | Pro | Asn |      |
|            |             |            |            | 140        |             |     |     |     | 145 |            |            |     |     | 150 |     |      |
| aat        | aga         | cat        | gct        | tat        | gta         | ggg | att | gct | gtg | att        | tgg        | gtc | ctt | gct | gtg | 772  |
| Asn        | Arg         | His        | Ala        | Tyr        | Val         | Gly | Ile | Ala | Val | Ile        | Trp        | Val | Leu | Ala | Val |      |
|            |             |            |            | 155        |             |     |     | 160 |     |            |            |     |     | 165 |     |      |
| gct        | tct         | tct        | ttg        | cct        | ttc         | ctg | atc | tac | caa | gta        | atg        | act | gat | gag | ccg | 820  |
| Ala        | Ser         | Ser        | Leu        | Pro        | Phe         | Leu | Ile | Tyr | Gln | Val        | Met        | Thr | Asp | Glu | Pro |      |
|            |             |            |            | 170        |             |     |     | 175 |     |            |            |     | 180 |     |     |      |
| ttc        | caa         | aat        | gta        | aca        | ctt         | gat | gcg | tac | aaa | gac        | aaa        | tac | gtg | tgc | ttt | 868  |
| Phe        | Gln         | Asn        | Val        | Thr        | Leu         | Asp | Ala | Tyr | Lys | Asp        | Lys        | Tyr | Val | Cys | Phe |      |
|            |             |            |            | 185        |             |     | 190 |     |     |            | 195        |     |     |     |     |      |
| gat        | caa         | ttt        | cca        | tcg        | gac         | tct | cat | agg | ttg | tct        | tat        | acc | act | ctc | ctc | 916  |
| Asp        | Gln         | Phe        | Pro        | Ser        | Asp         | Ser | His | Arg | Leu | Ser        | Tyr        | Thr | Thr | Leu | Leu |      |
| 200        |             |            |            |            | 205         |     |     |     |     | 210        |            |     |     |     | 215 |      |
| ttg        | gtg         | ctg        | cag        | tat        | ttt         | ggg | cca | ctt | tgt | ttt        | ata        | ttt | att | tgc | tac | 964  |
| Leu        | Val         | Leu        | Gln        | Tyr        | Phe         | Gly | Pro | Leu | Cys | Phe        | Ile        | Phe | Ile | Cys | Tyr |      |
|            |             |            |            | 220        |             |     |     |     | 225 |            |            |     |     | 230 |     |      |
| ttc        | aag         | ata        | tat        | ata        | cgc         | cta | aaa | agg | aga | aac        | aac        | atg | atg | gac | aag | 1012 |
| Phe        | Lys         | Ile        | Tyr        | Ile        | Arg         | Leu | Lys | Arg | Arg | Asn        | Asn        | Met | Met | Asp | Lys |      |
|            |             |            |            | 235        |             |     |     | 240 |     |            |            |     | 245 |     |     |      |
| atg        | aga         | gac        | aat        | aag        | tac         | agg | tcc | agt | gaa | acc        | aaa        | aga | atc | aat | atc | 1060 |
| Met        | Arg         | Asp        | Asn        | Lys        | Tyr         | Arg | Ser | Ser | Glu | Thr        | Lys        | Arg | Ile | Asn | Ile |      |
|            |             |            |            | 250        |             |     | 255 |     |     |            |            | 260 |     |     |     |      |
| atg        | ctg         | ctc        | tcc        | att        | gtg         | gta | gca | ttt | gca | gtc        | tgc        | tgg | ctc | cct | ctt | 1108 |
| Met        | Leu         | Leu        | Ser        | Ile        | Val         | Val | Ala | Phe | Ala | Val        | Cys        | Trp | Leu | Pro | Leu |      |
|            |             |            |            |            |             | 270 |     |     |     |            | 275        |     |     |     |     |      |
| acc        | atc         | ttt        | aac        | act        | gtg         | ttt | gat | tgg | aat | cat        | cag        | atc | att | gct | acc | 1156 |
| Thr        | Ile         | Phe        | Asn        | Thr        | Val         | Phe | Asp | Trp | Asn | His        | Gln        | Ile | Ile | Ala | Thr |      |
| 280        |             |            |            |            | 285         |     |     |     |     | 290        |            |     |     |     | 295 |      |
| tgc        | aac         | cac        | aat        | ctg        | tta         | ttc | ctg | ctc | tgc | cac        | ctc        | aca | gca | atg | ata | 1204 |
| Cys        | Asn         | His        | Asn        | Leu        | Leu         | Phe | Leu | Leu | Cys | His        | Leu        | Thr | Ala | Met | Ile |      |
|            |             |            |            | 300        |             |     |     |     | 305 |            |            |     |     | 310 |     |      |
| tcc        | act         | tgt        | gtc        | aac        | ccc         | ata | ttt | tat | ggg | ttc        | ctg        | aac | aaa | aac | ttc | 1252 |
| Ser        | Thr         | Cys        | Val        | Asn        | Pro         | Ile | Phe | Tyr | Gly | Phe        | Leu        | Asn | Lys | Asn | Phe |      |
|            |             |            |            | 315        |             |     |     | 320 |     |            |            |     | 325 |     |     |      |
| cag        | aga         | gac        | ttg        | cag        | ttc         | ttc | ttc | aac | ttt | tgt        | gat        | ttc | cgg | tct | cgg | 1300 |
| Gln        | Arg         | Asp        | Leu        | Gln        | Phe         | Phe | Phe | Asn | Phe | Cys        | Asp        | Phe | Arg | Ser | Arg |      |
|            |             |            | 330        |            |             |     | 335 |     |     |            |            | 340 |     |     |     |      |
| gat        | gat         | gat        | tat        | gaa        | aca         | ata | gcc | atg | tcc | acg        | atg        | cac | aca | gat | gtt | 1348 |
| Asp        | Asp         | Asp        | Tyr        | Glu        | Thr         | Ile | Ala | Met | Ser | Thr        | Met        | His | Thr | Asp | Val |      |
|            |             |            |            | 345        |             |     | 350 |     |     |            | 355        |     |     |     |     |      |
| tcc        | aaa         | act        | tct        | ttg        | aag         | caa | gca | agc | cca | gtc        | gca        | ttt | aaa | aaa | atc | 1396 |
| Ser        | Lys         | Thr        | Ser        | Leu        | Lys         | Gln | Ala | Ser | Pro | Val        | Ala        | Phe | Lys | Lys | Ile |      |
|            |             |            |            |            | 365         |     |     |     |     | 370        |            |     |     |     | 375 |      |
| aac        | aac         | aat        | gat        | gat        | aat         | gaa | aaa | atc | tga | aactacttat | agcctatggt |     |     |     |     | 1446 |
| Asn        | Asn         | Asn        | Asp        | Asp        | Asn         | Glu | Lys | Ile | *   |            |            |     |     |     |     |      |
|            |             |            |            | 380        |             |     |     |     |     |            |            |     |     |     |     |      |
| cccggatgac | atctgttttaa | aaacaagcac | aacctgcaac | atactttgat | tacctgttct  |     |     |     |     |            |            |     |     |     |     | 1506 |
| cccaaggaat | ggggttgaaa  | tcatttgaaa | atgactaaga | ttttcttgtc | ttgcttttta  |     |     |     |     |            |            |     |     |     |     | 1566 |
| ctgcttttgt | tgtagttgtc  | ataattacat | ttggaacaaa | aggtgtgggc | tttgggggtct |     |     |     |     |            |            |     |     |     |     | 1626 |

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tctggaaata gttttgacca gacatctttg aagtgccttt tgtgaattta tgcataataat 1686
ataaagactt ttatactgta cttattggaa tgaaatttct ttaaagtatt actattaact 1746
gacttcagaa gtacctgccca tccaatacgg tcattagatt gggtcacctt gattagatta 1806
gattagatta gattgtcaac agattgggcc atccttactt tatgataggc atcattttag 1866
tgtgttacaa tagtaacagt atgcaaaagc agcattcagg agccgaaaga tagtctgaag 1926
tcattcagaa gtggtttgag gtttctgttt tttgggtggt tttgtttgtt tttttttttt 1986
caccttaagg gaggatttaa tttgctccca actgattgtc acttaaatga aaatttaaaa 2046
atgaataaaa agacatactt ctcagctgca aatattatgg agaattgggg caccacagg 2106
aatgaagaga gaaagcagct ccctaacttc aaaaccattt tggtagctga caacaagagc 2166
attttagagt aattaattta ataaagtaaa ttagtattgc tgcaaatagc taaattatat 2226
ttatttgaat tgatggtcaa gagattttcc atttttttta cagactgttc agtgtttgtc 2286
aagctttctg gcataaatat gtactcaaaa ggcatttccg cttacaattt gtagaaacac 2346
aaaaatgcgtt ttccatacag cagtgcctat atagtgactg atttttaact ttcaatgtcc 2406
atctttcaaa ggaagtaaca ccaaggtaac atgttaaagg aatattcact ttacctagca 2466
gggaaaaata cacaaaaact gcagatactt catatagccc attttaactt gtataaactg 2526
tgtgacttgt ggcgctctat aaataatgca ctgtaaagat tactgaatag ttgtgtcatg 2586
ttaatgtgcc taatttcagt tatcttgtaa tcatgattga gcctcagaat catttggaga 2646
aactatattt taaagaacaa gacatacttc aatgtattat acagataaag tattacatgt 2706
gtttgatattt aaaagggcgg acattttatt aaaatcaata ttgtttttgc tttttcaaaa 2766
aaaaaaaaaa aa 2778

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<210> SEQ ID NO 28
<211> LENGTH: 384
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 28

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Met Asn Ser Thr Leu Phe Ser Gln Val Glu Asn His Ser Val His Ser
1           5           10           15
Asn Phe Ser Glu Lys Asn Ala Gln Leu Leu Ala Phe Glu Asn Asp Asp
20          25          30
Cys His Leu Pro Leu Ala Met Ile Phe Thr Leu Ala Leu Ala Tyr Gly
35          40          45
Ala Val Ile Ile Leu Gly Val Ser Gly Asn Leu Ala Leu Ile Ile Ile
50          55          60
Ile Leu Lys Gln Lys Glu Met Arg Asn Val Thr Asn Ile Leu Ile Val
65          70          75          80
Asn Leu Ser Phe Ser Asp Leu Leu Val Ala Ile Met Cys Leu Pro Phe
85          90          95
Thr Phe Val Tyr Thr Leu Met Asp His Trp Val Phe Gly Glu Ala Met
100         105         110
Cys Lys Leu Asn Pro Phe Val Gln Cys Val Ser Ile Thr Val Ser Ile
115         120         125
Phe Ser Leu Val Leu Ile Ala Val Glu Arg His Gln Leu Ile Ile Asn
130         135         140

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Arg | Gly | Trp | Arg | Pro | Asn | Asn | Arg | His | Ala | Tyr | Val | Gly | Ile | Ala |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Val | Ile | Trp | Val | Leu | Ala | Val | Ala | Ser | Ser | Leu | Pro | Phe | Leu | Ile | Tyr |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Gln | Val | Met | Thr | Asp | Glu | Pro | Phe | Gln | Asn | Val | Thr | Leu | Asp | Ala | Tyr |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Lys | Asp | Lys | Tyr | Val | Cys | Phe | Asp | Gln | Phe | Pro | Ser | Asp | Ser | His | Arg |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Leu | Ser | Tyr | Thr | Thr | Leu | Leu | Leu | Val | Leu | Gln | Tyr | Phe | Gly | Pro | Leu |
|     | 210 |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |     |
| Cys | Phe | Ile | Phe | Ile | Cys | Tyr | Phe | Lys | Ile | Tyr | Ile | Arg | Leu | Lys | Arg |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Arg | Asn | Asn | Met | Met | Asp | Lys | Met | Arg | Asp | Asn | Lys | Tyr | Arg | Ser | Ser |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     |     | 255 |     |
| Glu | Thr | Lys | Arg | Ile | Asn | Ile | Met | Leu | Leu | Ser | Ile | Val | Val | Ala | Phe |
|     |     |     | 260 |     |     |     | 265 |     |     |     |     |     | 270 |     |     |
| Ala | Val | Cys | Trp | Leu | Pro | Leu | Thr | Ile | Phe | Asn | Thr | Val | Phe | Asp | Trp |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Asn | His | Gln | Ile | Ile | Ala | Thr | Cys | Asn | His | Asn | Leu | Leu | Phe | Leu | Leu |
|     | 290 |     |     |     | 295 |     |     |     |     |     | 300 |     |     |     |     |
| Cys | His | Leu | Thr | Ala | Met | Ile | Ser | Thr | Cys | Val | Asn | Pro | Ile | Phe | Tyr |
| 305 |     |     |     | 310 |     |     |     |     |     | 315 |     |     |     |     | 320 |
| Gly | Phe | Leu | Asn | Lys | Asn | Phe | Gln | Arg | Asp | Leu | Gln | Phe | Phe | Phe | Asn |
|     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |
| Phe | Cys | Asp | Phe | Arg | Ser | Arg | Asp | Asp | Asp | Tyr | Glu | Thr | Ile | Ala | Met |
|     |     | 340 |     |     |     |     | 345 |     |     |     |     |     | 350 |     |     |
| Ser | Thr | Met | His | Thr | Asp | Val | Ser | Lys | Thr | Ser | Leu | Lys | Gln | Ala | Ser |
|     | 355 |     |     |     |     | 360 |     |     |     |     |     | 365 |     |     |     |
| Pro | Val | Ala | Phe | Lys | Lys | Ile | Asn | Asn | Asn | Asp | Asp | Asn | Glu | Lys | Ile |
|     | 370 |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |     |

<210> SEQ ID NO 29  
 <211> LENGTH: 2881  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (241) ... (1005)

<400> SEQUENCE: 29

|                                                                    |     |
|--------------------------------------------------------------------|-----|
| ttttcacttt aaagagtctt gtgagtcaga agtcattttg actgccctca ataaaattag  | 60  |
| taatgcaatt gggtcattttc tctttacaga ttgttcagtt caagggaatg aagaattcag | 120 |
| aataattttg gtaaatggat tccaatatcg ggaataagaa taagctgaac agttgacctg  | 180 |
| ctttgaagaa acatactgtc catttgtcta aaataatcta taacaaccaa accaatcaaa  | 240 |
| atg aat tca aca tta ttt tcc cag gtt gaa aat cat tca gtc cac tct    | 288 |
| Met Asn Ser Thr Leu Phe Ser Gln Val Glu Asn His Ser Val His Ser    |     |
| 1 5 10 15                                                          |     |
| aat ttc tca gag aag aat gcc cag ctt ctg gct ttt gaa aat gat gat    | 336 |
| Asn Phe Ser Glu Lys Asn Ala Gln Leu Leu Ala Phe Glu Asn Asp Asp    |     |
| 20 25 30                                                           |     |
| tgt cat ctg ccc ttg gcc atg ata ttt acc tta gct ctt gct tat gga    | 384 |
| Cys His Leu Pro Leu Ala Met Ile Phe Thr Leu Ala Leu Ala Tyr Gly    |     |
| 35 40 45                                                           |     |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| gct gtg atc att ctt ggt gtc tct gga aac ctg gcc ttg atc ata atc    | 432  |
| Ala Val Ile Ile Leu Gly Val Ser Gly Asn Leu Ala Leu Ile Ile Ile    |      |
| 50 55 60                                                           |      |
| atc ttg aaa caa aag gag atg aga aat gtt acc aac atc ctg att gtg    | 480  |
| Ile Leu Lys Gln Lys Glu Met Arg Asn Val Thr Asn Ile Leu Ile Val    |      |
| 65 70 75 80                                                        |      |
| aac ctt tcc ttc tca gac ttg ctt gtt gcc atc atg tgt ctc ccc ttt    | 528  |
| Asn Leu Ser Phe Ser Asp Leu Leu Val Ala Ile Met Cys Leu Pro Phe    |      |
| 85 90 95                                                           |      |
| aca ttt gtc tac aca tta atg gac cac tgg gtc ttt ggt gag gcg atg    | 576  |
| Thr Phe Val Tyr Thr Leu Met Asp His Trp Val Phe Gly Glu Ala Met    |      |
| 100 105 110                                                        |      |
| tgt aag ttg aat cct ttt gtg caa tgt gtt tca atc act gtg tcc att    | 624  |
| Cys Lys Leu Asn Pro Phe Val Gln Cys Val Ser Ile Thr Val Ser Ile    |      |
| 115 120 125                                                        |      |
| ttc tct ctg gtt ctc att gct gtg gaa cga cat cag ctg ata atc aac    | 672  |
| Phe Ser Leu Val Leu Ile Ala Val Glu Arg His Gln Leu Ile Ile Asn    |      |
| 130 135 140                                                        |      |
| cct cga ggg tgg aga cca aat aat aga cat gct tat gta ggt att gct    | 720  |
| Pro Arg Gly Trp Arg Pro Asn Asn Arg His Ala Tyr Val Gly Ile Ala    |      |
| 145 150 155 160                                                    |      |
| gtg att tgg gtc ctt gct gtg gct tct tct ttg cct ttc ctg atc tac    | 768  |
| Val Ile Trp Val Leu Ala Val Ala Ser Ser Leu Pro Phe Leu Ile Tyr    |      |
| 165 170 175                                                        |      |
| caa gta atg act gat gag cgg ttc caa aat gta aca ctt gat gcg tac    | 816  |
| Gln Val Met Thr Asp Glu Pro Phe Gln Asn Val Thr Leu Asp Ala Tyr    |      |
| 180 185 190                                                        |      |
| aaa gac aaa tac gtg tgc ttt gat caa ttt cca tgc gac tct cat agg    | 864  |
| Lys Asp Lys Tyr Val Cys Phe Asp Gln Phe Pro Ser Asp Ser His Arg    |      |
| 195 200 205                                                        |      |
| ttg tct tat acc act ctc ctc ttg gtg ctg cag tat ttt ggt cca ctt    | 912  |
| Leu Ser Tyr Thr Thr Leu Leu Val Leu Gln Tyr Phe Gly Pro Leu        |      |
| 210 215 220                                                        |      |
| tgt ttt ata ttt att tgc tac ttc aag gta aga aaa ctt ttt ttc tat    | 960  |
| Cys Phe Ile Phe Ile Cys Tyr Phe Lys Val Arg Lys Leu Phe Phe Tyr    |      |
| 225 230 235 240                                                    |      |
| cat ttc cat ttt tac ctt ctt tac aca gaa ttc ctc atc aaa tga        | 1005 |
| His Phe His Phe Tyr Leu Leu Tyr Thr Glu Phe Leu Ile Lys *          |      |
| 245 250                                                            |      |
| gtgtttctat ttaaactttt ttcttcata gatatatata cgctaaaaa ggagaaacaa    | 1065 |
| catgatggac aagatgagag acaataagta caggtccagt gaaacccaaa gaatcaatat  | 1125 |
| catgtctgctc tccattgtgg tagcatttgc agtctgctgg ctccctctta ccacttttaa | 1185 |
| cactgtgttt gattggaatc atcagatcat tgctacctgc aaccacaatc tgttattcct  | 1245 |
| gctctgccac ctcacagcaa tgatatccac ttgtgtcaac cccatatattt atgggttcct | 1305 |
| gaacaaaaac ttccagagag acttgcagtt cttcttcaac ttttgtgatt tccggtctcg  | 1365 |
| ggatgatgat tatgaaacaa tagccatgtc cacgatgcac acagatgttt ccaaaaacttc | 1425 |
| tttgaagcaa gcaagcccag tcgcatTTaa aaaaaatcaac aacaatgatg ataatgaaaa | 1485 |
| aatctgaaac tacttatagc ctatgggtccc ggatgacatc tgtttaaaaa caagcacaac | 1545 |
| ctgcaacata ctttgattac ctgttctccc aaggaatggg gttgaaatca tttgaaatg   | 1605 |
| actaagattt tcttgtcttg ctttttactg cttttgttgt agttgtcata attacatttg  | 1665 |
| gaacaaaagg tgtgggcttt ggggtcttct ggaaatagtt ttgaccagac atctttgaag  | 1725 |

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tgctttttgt gaatttatgc atataatata aagactttta tactgtactt attggaatga 1785
aattttctta aagtattacg atgcgctgac ttcagaagta cctgccatcc aatacgggtca 1845
ttagattggg tcatcttgat tagattagat tagattagat tgtcaacaga ttggggccatc 1905
cttactttat gataggcatc attttagtgt gttacaatag taacagtatg caaaagcagc 1965
attcaggagc cgaaagatag tcttgaagtc attcagaagt ggtttgaggt ttctgttttt 2025
tgggtggttt tgtttgtttt tttttttttt caccttaagg gaggctttca ttctctcccg 2085
actgattgtc acttaaatca aaatttataa atgaataaaa agacatactt ctcagctgca 2145
aatattatgg agaattgggc acccacagga atgaagagag aaagcagctc cccaacttca 2205
aaaccatttt ggtacctgac aacaagagca ttttagagta attaatttaa taaagtaa 2265
tagtattgct gcaaatagct aaattatatt tatttgaatt gatgggtcaag agattttcca 2325
ttttttttac agactgttca gtgtttgtca agcttctggt ctaatatgta ctgaaagac 2385
tttcgctta caattttag aaacacaaat atcgttttcc atacagcagt gcctatatag 2445
tgactgattt taactttcaa tgtccatctt tcaaaggaag taacaccaag gtacaatgtt 2505
aaaggaatat tcactttacc tagcagggaa aaatacacia aaactgcaga tacttcatat 2565
agcccathtt aacttgata aactgtgtga cttgtggcgt cttataaata atgcactgta 2625
aagattactg aatagttgtg tcatgttaat gtgcctaatt tcatgtatct tgtaatcatg 2685
attgagcctc agaatcattt ggagaaacta tattttaaag aacaagacat acttcaatgt 2745
attatacaga taaagtatta catgtgtttg attttaaaag ggcggacatt ttattaaaat 2805
caatattggt tttgcttttt ctgaggagtc tctttcagtt tcattttttc tcatcccatg 2865
acttccctcc gatggt 2881

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<210> SEQ ID NO 30
<211> LENGTH: 254
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 30

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Met Asn Ser Thr Leu Phe Ser Gln Val Glu Asn His Ser Val His Ser
1           5           10          15
Asn Phe Ser Glu Lys Asn Ala Gln Leu Leu Ala Phe Glu Asn Asp Asp
20          25          30
Cys His Leu Pro Leu Ala Met Ile Phe Thr Leu Ala Leu Ala Tyr Gly
35          40          45
Ala Val Ile Ile Leu Gly Val Ser Gly Asn Leu Ala Leu Ile Ile Ile
50          55          60
Ile Leu Lys Gln Lys Glu Met Arg Asn Val Thr Asn Ile Leu Ile Val
65          70          75          80
Asn Leu Ser Phe Ser Asp Leu Leu Val Ala Ile Met Cys Leu Pro Phe
85          90          95
Thr Phe Val Tyr Thr Leu Met Asp His Trp Val Phe Gly Glu Ala Met
100         105         110
Cys Lys Leu Asn Pro Phe Val Gln Cys Val Ser Ile Thr Val Ser Ile
115         120         125
Phe Ser Leu Val Leu Ile Ala Val Glu Arg His Gln Leu Ile Ile Asn
130         135         140
Pro Arg Gly Trp Arg Pro Asn Asn Arg His Ala Tyr Val Gly Ile Ala

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|                                                                 |                                                     |                         |     |
|-----------------------------------------------------------------|-----------------------------------------------------|-------------------------|-----|
| 145                                                             | 150                                                 | 155                     | 160 |
| Val Ile Trp                                                     | Val Leu Ala Val Ala Ser Ser                         | Leu Pro Phe Leu Ile Tyr |     |
|                                                                 | 165                                                 | 170                     | 175 |
| Gln Val Met                                                     | Thr Asp Glu Pro Phe Gln Asn Val Thr Leu Asp Ala Tyr |                         |     |
|                                                                 | 180                                                 | 185                     | 190 |
| Lys Asp Lys Tyr Val Cys Phe Asp Gln Phe Pro Ser Asp Ser His Arg |                                                     |                         |     |
|                                                                 | 195                                                 | 200                     | 205 |
| Leu Ser Tyr Thr Thr Leu Leu Leu Val Leu Gln Tyr Phe Gly Pro Leu |                                                     |                         |     |
|                                                                 | 210                                                 | 215                     | 220 |
| Cys Phe Ile Phe Ile Cys Tyr Phe Lys Val Arg Lys Leu Phe Phe Tyr |                                                     |                         |     |
|                                                                 | 225                                                 | 230                     | 235 |
| His Phe His Phe Tyr Leu Leu Tyr Thr Glu Phe Leu Ile Lys         |                                                     |                         |     |
|                                                                 | 245                                                 | 250                     |     |

<210> SEQ ID NO 31  
 <211> LENGTH: 2492  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (272) ... (700)

<400> SEQUENCE: 31

|                                                                    |     |
|--------------------------------------------------------------------|-----|
| agcggaatct ttaggatctg agcaggagaa ataccagcgg atcttcccca ctctgctccc  | 60  |
| ttccattccc acccttcctt ctttaataag caggagcgaa aaagacaaat tccaaagagg  | 120 |
| attgttcagt tcaagggaat gaagaattca gaataatttt ggtaaattgga ttccaatatg | 180 |
| gggaataaga ataagctgaa cagttgacct gctttgaaga aacatactgt ccatttgtct  | 240 |
| aaaataatct ataacaacca aaccaatcaa a atg aat tca aca tta ttt tcc     | 292 |
| Met Asn Ser Thr Leu Phe Ser                                        |     |
| 1 5                                                                |     |
| cag gtt gaa aat cat tca gtc cac tct aat ttc tca gag aag aat gcc    | 340 |
| Gln Val Glu Asn His Ser Val His Ser Asn Phe Ser Glu Lys Asn Ala    |     |
| 10 15 20                                                           |     |
| cag ctt ctg gct ttt gaa aat gat gat tgt cat ctg ccc ttg gcc atg    | 388 |
| Gln Leu Leu Ala Phe Glu Asn Asp Asp Cys His Leu Pro Leu Ala Met    |     |
| 25 30 35                                                           |     |
| ata ttt acc tta gct ctt gct tat gga gct gtg atc att ctt ggt gtc    | 436 |
| Ile Phe Thr Leu Ala Leu Ala Tyr Gly Ala Val Ile Ile Leu Gly Val    |     |
| 40 45 50 55                                                        |     |
| tct gga aac ctg gcc ttg atc ata atc atc ttg aaa caa aag gag atg    | 484 |
| Ser Gly Asn Leu Ala Leu Ile Ile Ile Ile Leu Lys Gln Lys Glu Met    |     |
| 60 65 70                                                           |     |
| aga aat gtt acc aac atc ctg att gtg aac ctt tcc ttc tca gac ttg    | 532 |
| Arg Asn Val Thr Asn Ile Leu Ile Val Asn Leu Ser Phe Ser Asp Leu    |     |
| 75 80 85                                                           |     |
| ctt gtt gcc atc atg tgt ctc ccc ttt aca ttt gtc tac aca tta atg    | 580 |
| Leu Val Ala Ile Met Cys Leu Pro Phe Thr Phe Val Tyr Thr Leu Met    |     |
| 90 95 100                                                          |     |
| gac cac tgg gtc ttt ggt gag gcg atg tgt tgt ctt ata cca ctc tcc    | 628 |
| Asp His Trp Val Phe Gly Glu Ala Met Cys Cys Leu Ile Pro Leu Ser    |     |
| 105 110 115                                                        |     |
| tct tgg tgc tgc agt att ttg gtc cac ttt gtt tta tat tta ttt gct    | 676 |
| Ser Trp Cys Cys Ser Ile Leu Val His Phe Val Leu Tyr Leu Phe Ala    |     |
| 120 125 130 135                                                    |     |
| act tca aga tat ata tac gcc taa aaaggagaaa caacatgatg gacaagatga   | 730 |

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Thr Ser Arg Tyr Ile Tyr Ala \*  
140

gagacaataa gtacaggtcc agtgaacca aaagaatcaa tatcatgctg ctctccattg 790  
 tggtagcatt tgcagctgc tggctccctc ttaccatctt taacactgtg ttgattgga 850  
 atcatcagat cattgctacc tgcaaccaca atctgttatt cctgctctgc cacctcacag 910  
 caatgatatc cacttggtgc aaccccatat tttatgggtt cctgaacaaa aacttccaga 970  
 gagacttgca gttcttcttc aacttttgtg atttccggtc tcgggatgat gattatgaaa 1030  
 caatagccat gtccacgatg cacacagatg tttccaaaac ttctttgaag caagcaagcc 1090  
 cagtcgcatt taaaaaatc aacaacaatg atgataatga aaaaatctga aactacttat 1150  
 agcctatggt cccggatgac atctgtttaa aaacaagcac aacctgcaac atactttgat 1210  
 tacctgttct cccaaggaat ggggttgaaa tcatttgaaa atgactaaga ttttcttgtc 1270  
 ttgcttttta ctgcttttgt tgtagtgtgc ataattacat ttggaacaaa aggtgtgggc 1330  
 tttgggtct tctggaata gttttgacca gacatctttg aagtgtttt tgtgaattta 1390  
 tgcataaat ataaagactt ttatactgta cttattggaa tgaaatttct ttaaagtatt 1450  
 actattaact gacttcagaa gtacctgcca tccaatacgg tcattagatt gggtcactt 1510  
 gattagatta gattagatta gattgtcaac agattgggcc atccttactt tatgataggc 1570  
 atcattttag tgtgttcaaa tagtaacagt atgcaaaagc agcattcagg agccgaaga 1630  
 tagtctgaag tcattcagaa gtggtttgag gtttctgttt tttggtggtt tttgtttgtt 1690  
 tttttttttt cacttaagg gaggatttaa tttgtccca actgattgtc acttaaatga 1750  
 aaatttaaaa atgaataaaa agacatactt ctgagctgca aatattatgg agaattgggg 1810  
 caccacagc aatgaagaga gaaagcagct ccctaacttc aaaaccattt tggtagctga 1870  
 caacaagagc atttttagt aattaattta ataaagtaa ttagtattgc tgcaaatagc 1930  
 taaattatat ttatttgaat tgatggtcaa gagattttcc atttttttta cagactgttc 1990  
 agtgtttgtc aagctttctg gcataaatat gtactcaaaa ggcatttccg cttacaattt 2050  
 gtagaaacac aaaatgcgtt ttccatacag cagtccttat atagtactg atttttaact 2110  
 ttcaatgtcc atctttcaaa ggaagtaaca ccaaggtaca atgttaaagg aatattcact 2170  
 ttacctagca gggaaaaata cacaaaaact gcagatactt catatagccc attttaactt 2230  
 gtataaactg tgtgacttgt ggcgtcttat aaataatgca ctgtaaagat tactgaatag 2290  
 ttgtgtcatg ttaatgtgcc taatttcatt tatcttgtaa tcatgattga gctcagaat 2350  
 catttgga aactatattt taaagaacaa gacatacttc aatgtattat acagataaag 2410  
 tattacatgt gtttgatttt aaaagggcgg acattttatt aaaatcaata ttgtttttgc 2470  
 tttttcaaaa aaaaaaaaaa aa 2492

<210> SEQ ID NO 32  
 <211> LENGTH: 142  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 32

Met Asn Ser Thr Leu Phe Ser Gln Val Glu Asn His Ser Val His Ser  
 1 5 10 15

Asn Phe Ser Glu Lys Asn Ala Gln Leu Leu Ala Phe Glu Asn Asp Asp  
 20 25 30

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Cys His Leu Pro Leu Ala Met Ile Phe Thr Leu Ala Leu Ala Tyr Gly  
 35 40 45  
 Ala Val Ile Ile Leu Gly Val Ser Gly Asn Leu Ala Leu Ile Ile Ile  
 50 55 60  
 Ile Leu Lys Gln Lys Glu Met Arg Asn Val Thr Asn Ile Leu Ile Val  
 65 70 75 80  
 Asn Leu Ser Phe Ser Asp Leu Leu Val Ala Ile Met Cys Leu Pro Phe  
 85 90 95  
 Thr Phe Val Tyr Thr Leu Met Asp His Trp Val Phe Gly Glu Ala Met  
 100 105 110  
 Cys Cys Leu Ile Pro Leu Ser Ser Trp Cys Cys Ser Ile Leu Val His  
 115 120 125  
 Phe Val Leu Tyr Leu Phe Ala Thr Ser Arg Tyr Ile Tyr Ala  
 130 135 140

<210> SEQ ID NO 33  
 <211> LENGTH: 4458  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (100)...(4125)

<400> SEQUENCE: 33

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ctagtctata ccagcaacga ctctacatc gtccactctg gggatcttag aaagatccat      60
aaagctgcct cccggggaca agtccggaag ctggagaag atg aca aag agg aag      114
                               Met Thr Lys Arg Lys
                               1           5
aag acc atc aac ctt aat ata caa gac gcc cag aag agg act gct cta      162
Lys Thr Ile Asn Leu Asn Ile Gln Asp Ala Gln Lys Arg Thr Ala Leu
                10                15                20
cac tgg gcc tgt gtc aat ggc cat gag gaa gta gta aca ttt ctg gta      210
His Trp Ala Cys Val Asn Gly His Glu Glu Val Val Thr Phe Leu Val
                25                30                35
gac aga aag tgc cag ctt gac gtc ctt gat ggc gaa cac agg aca cct      258
Asp Arg Lys Cys Gln Leu Asp Val Leu Asp Gly Glu His Arg Thr Pro
                40                45                50
ctg atg aag gct cta caa tgc cat cag gag gct tgt gca aat att ctg      306
Leu Met Lys Ala Leu Gln Cys His Gln Glu Ala Cys Ala Asn Ile Leu
                55                60                65
ata gat tct ggt gcc gat ata aat ctc gta gat gtg tat ggc aac atg      354
Ile Asp Ser Gly Ala Asp Ile Asn Leu Val Asp Val Tyr Gly Asn Met
                70                75                80                85
gct ctc cat tat gct gtt tat agt gag att ttg tca gtg gtg gca aaa      402
Ala Leu His Tyr Ala Val Tyr Ser Glu Ile Leu Ser Val Val Ala Lys
                90                95                100
ctg ctg tcc cat ggt gca gtc atc gaa gtg cac aac aag gct agc ctc      450
Leu Leu Ser His Gly Ala Val Ile Glu Val His Asn Lys Ala Ser Leu
                105                110                115
aca cca ctt tta cta tcc ata acg aaa aga agt gag caa att gtg gaa      498
Thr Pro Leu Leu Ser Ile Thr Lys Arg Ser Glu Gln Ile Val Glu
                120                125                130
ttt ttg ctg ata aaa aat gca aat gcg aat gca gtt aat aag tat aaa      546
Phe Leu Leu Ile Lys Asn Ala Asn Ala Asn Ala Val Asn Lys Tyr Lys
                135                140                145
tgc aca gcc ctc atg ctt gct gta tgt cat gga tca tca gag ata gtt      594

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| Cys Thr Ala Leu Met Leu Ala Val Cys His Gly Ser Ser Glu Ile Val |      |
| 150 155 160 165                                                 |      |
| ggc atg ctt ctt cag caa aat gtt gac gtc ttt gct gca gat ata tgt | 642  |
| Gly Met Leu Leu Gln Gln Asn Val Asp Val Phe Ala Ala Asp Ile Cys |      |
| 170 175 180                                                     |      |
| gga gta act gca gaa cat tat gct gtt act tgt gga ttt cat cac att | 690  |
| Gly Val Thr Ala Glu His Tyr Ala Val Thr Cys Gly Phe His His Ile |      |
| 185 190 195                                                     |      |
| cat gaa caa att atg gaa tat ata cga aaa tta tct aaa aat cat caa | 738  |
| His Glu Gln Ile Met Glu Tyr Ile Arg Lys Leu Ser Lys Asn His Gln |      |
| 200 205 210                                                     |      |
| aat acc aat cca gaa gga aca tct gca gga aca cct gat gag gct gca | 786  |
| Asn Thr Asn Pro Glu Gly Thr Ser Ala Gly Thr Pro Asp Glu Ala Ala |      |
| 215 220 225                                                     |      |
| ccc ttg gcg gaa aga aca cct gac aca gct gaa agc ttg gtg gaa aaa | 834  |
| Pro Leu Ala Glu Arg Thr Pro Asp Thr Ala Glu Ser Leu Val Glu Lys |      |
| 230 235 240 245                                                 |      |
| aca cct gat gag gct gca ccc ttg gtg gaa aga aca cct gac acg gct | 882  |
| Thr Pro Asp Glu Ala Ala Pro Leu Val Glu Arg Thr Pro Asp Thr Ala |      |
| 250 255 260                                                     |      |
| gaa agc ttg gtg gaa aaa aca cct gat gag gct gca tcc ttg gtg gag | 930  |
| Glu Ser Leu Val Glu Lys Thr Pro Asp Glu Ala Ala Ser Leu Val Glu |      |
| 265 270 275                                                     |      |
| gga aca tct gac aaa att caa tgt ttg gag aaa gcg aca tct gga aag | 978  |
| Gly Thr Ser Asp Lys Ile Gln Cys Leu Glu Lys Ala Thr Ser Gly Lys |      |
| 280 285 290                                                     |      |
| ttc gaa cag tca gca gaa gaa aca cct agg gaa att acg agt cct gca | 1026 |
| Phe Glu Gln Ser Ala Glu Glu Thr Pro Arg Glu Ile Thr Ser Pro Ala |      |
| 295 300 305                                                     |      |
| aaa gaa aca tct gag aaa ttt acg tgg cca gca aaa gga aga cct agg | 1074 |
| Lys Glu Thr Ser Glu Lys Phe Thr Trp Pro Ala Lys Gly Arg Pro Arg |      |
| 310 315 320 325                                                 |      |
| aag atc gca tgg gag aaa aaa gaa gac aca cct agg gaa att atg agt | 1122 |
| Lys Ile Ala Trp Glu Lys Lys Glu Asp Thr Pro Arg Glu Ile Met Ser |      |
| 330 335 340                                                     |      |
| ccc gca aaa gaa aca tct gag aaa ttt acg tgg gca gca aaa gga aga | 1170 |
| Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys Gly Arg |      |
| 345 350 355                                                     |      |
| cct agg aag atc gca tgg gag aaa aaa gaa aca cct gta aag act gga | 1218 |
| Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys Thr Gly |      |
| 360 365 370                                                     |      |
| tgc gtg gca aga gta aca tct aat aaa act aaa gtt ttg gaa aaa gga | 1266 |
| Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu Lys Gly |      |
| 375 380 385                                                     |      |
| aga tct aag atg att gca tgt cct aca aaa gaa tca tct aca aaa gca | 1314 |
| Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr Lys Ala |      |
| 390 395 400 405                                                 |      |
| agt gcc aat gat cag agg ttc cca tca gaa tcc aaa caa gag gaa gat | 1362 |
| Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu Glu Asp |      |
| 410 415 420                                                     |      |
| gaa gaa tat tct tgt gat tct cgg agt ctc ttt gag agt tct gca aag | 1410 |
| Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser Ala Lys |      |
| 425 430 435                                                     |      |
| att caa gtg tgt ata cct gag tct ata tat caa aaa gta atg gag ata | 1458 |
| Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met Glu Ile |      |
| 440 445 450                                                     |      |
| aat aga gaa gta gaa gag cct cct aag aag cca tct gcc ttc aag cct | 1506 |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Asn | Arg | Glu | Val | Glu | Glu | Pro | Pro | Lys | Lys | Pro | Ser | Ala | Phe | Lys | Pro |      |
| 455 |     |     |     |     |     | 460 |     |     |     | 465 |     |     |     |     |     |      |
| gcc | att | gaa | atg | caa | aac | tct | gtt | cca | aat | aaa | gcc | ttt | gaa | ttg | aag | 1554 |
| Ala | Ile | Glu | Met | Gln | Asn | Ser | Val | Pro | Asn | Lys | Ala | Phe | Glu | Leu | Lys |      |
| 470 |     |     |     |     | 475 |     |     |     |     | 480 |     |     |     |     | 485 |      |
| aat | gaa | caa | aca | ttg | aga | gca | gat | ccg | atg | ttc | cca | cca | gaa | tcc | aaa | 1602 |
| Asn | Glu | Gln | Thr | Leu | Arg | Ala | Asp | Pro | Met | Phe | Pro | Pro | Glu | Ser | Lys |      |
|     |     |     |     | 490 |     |     |     |     | 495 |     |     |     |     | 500 |     |      |
| caa | aag | gac | tat | gaa | gaa | aat | tct | tgg | gat | tct | gag | agt | ctc | tgt | gag | 1650 |
| Gln | Lys | Asp | Tyr | Glu | Glu | Asn | Ser | Trp | Asp | Ser | Glu | Ser | Leu | Cys | Glu |      |
|     |     |     | 505 |     |     |     |     | 510 |     |     |     |     | 515 |     |     |      |
| act | gtt | tca | cag | aag | gat | gtg | tgt | tta | ccc | aag | gct | aca | cat | caa | aaa | 1698 |
| Thr | Val | Ser | Gln | Lys | Asp | Val | Cys | Leu | Pro | Lys | Ala | Thr | His | Gln | Lys |      |
|     |     |     | 520 |     |     | 525 |     |     |     |     |     | 530 |     |     |     |      |
| gaa | ata | gat | aaa | ata | aat | gga | aaa | tta | gaa | gag | tct | cct | aat | aaa | gat | 1746 |
| Glu | Ile | Asp | Lys | Ile | Asn | Gly | Lys | Leu | Glu | Glu | Ser | Pro | Asn | Lys | Asp |      |
|     |     |     | 535 |     |     | 540 |     |     |     |     | 545 |     |     |     |     |      |
| ggc | ctt | ctg | aag | gct | acc | tgc | gga | atg | aaa | gtt | tct | att | cca | act | aaa | 1794 |
| Gly | Leu | Leu | Lys | Ala | Thr | Cys | Gly | Met | Lys | Val | Ser | Ile | Pro | Thr | Lys |      |
| 550 |     |     |     |     | 555 |     |     |     |     | 560 |     |     |     |     | 565 |      |
| gcc | tta | gaa | ttg | aag | gac | atg | caa | act | ttc | aaa | gag | gag | cct | ccg | ggg | 1842 |
| Ala | Leu | Glu | Leu | Lys | Asp | Met | Gln | Thr | Phe | Lys | Ala | Glu | Pro | Pro | Gly |      |
|     |     |     |     | 570 |     |     |     |     | 575 |     |     |     |     | 580 |     |      |
| aag | cca | tct | gcc | ttc | gag | cct | gcc | act | gaa | atg | caa | aag | tct | gtc | cca | 1890 |
| Lys | Pro | Ser | Ala | Phe | Glu | Pro | Ala | Thr | Glu | Met | Gln | Lys | Ser | Val | Pro |      |
|     |     |     | 585 |     |     |     |     | 590 |     |     |     |     |     | 595 |     |      |
| aat | aaa | gcc | ttg | gaa | ttg | aaa | aat | gaa | caa | aca | tgg | aga | gca | gat | gag | 1938 |
| Asn | Lys | Ala | Leu | Glu | Leu | Lys | Asn | Glu | Gln | Thr | Trp | Arg | Ala | Asp | Glu |      |
|     |     |     | 600 |     |     |     | 605 |     |     |     |     | 610 |     |     |     |      |
| ata | ctc | cca | tca | gaa | tcc | aaa | caa | aag | gac | tat | gaa | gaa | aat | tct | tgg | 1986 |
| Ile | Leu | Pro | Ser | Glu | Ser | Lys | Gln | Lys | Asp | Tyr | Glu | Glu | Asn | Ser | Trp |      |
|     |     |     | 615 |     |     | 620 |     |     |     |     | 625 |     |     |     |     |      |
| gat | act | gag | agt | ctc | tgt | gag | act | gtt | tca | cag | aag | gat | gtg | tgt | tta | 2034 |
| Asp | Thr | Glu | Ser | Leu | Cys | Glu | Thr | Val | Ser | Gln | Lys | Asp | Val | Cys | Leu |      |
| 630 |     |     |     |     | 635 |     |     |     |     | 640 |     |     |     |     | 645 |      |
| ccc | aag | gct | gag | cat | caa | aaa | gaa | ata | gat | aaa | ata | aat | gga | aaa | tta | 2082 |
| Pro | Lys | Ala | Ala | His | Gln | Lys | Glu | Ile | Asp | Lys | Ile | Asn | Gly | Lys | Leu |      |
|     |     |     |     | 650 |     |     |     |     | 655 |     |     |     |     | 660 |     |      |
| gaa | ggg | tct | cct | gtt | aaa | gat | ggc | ctt | ctg | aag | gct | aac | tgc | gga | atg | 2130 |
| Glu | Gly | Ser | Pro | Val | Lys | Asp | Gly | Leu | Leu | Lys | Ala | Asn | Cys | Gly | Met |      |
|     |     |     | 665 |     |     |     | 670 |     |     |     |     |     | 675 |     |     |      |
| aaa | gtt | tct | att | cca | act | aaa | gcc | tta | gaa | ttg | atg | gac | atg | caa | act | 2178 |
| Lys | Val | Ser | Ile | Pro | Thr | Lys | Ala | Leu | Glu | Leu | Met | Asp | Met | Gln | Thr |      |
|     |     |     | 680 |     |     |     | 685 |     |     |     |     | 690 |     |     |     |      |
| ttc | aaa | gca | gag | cct | ccc | gag | aag | cca | tct | gcc | ttc | gag | cct | gcc | att | 2226 |
| Phe | Lys | Ala | Glu | Pro | Pro | Glu | Lys | Pro | Ser | Ala | Phe | Glu | Pro | Ala | Ile |      |
|     |     |     | 695 |     |     | 700 |     |     |     |     | 705 |     |     |     |     |      |
| gaa | atg | caa | aag | tct | gtt | cca | aat | aaa | gcc | ttg | gaa | ttg | aag | aat | gaa | 2274 |
| Glu | Met | Gln | Lys | Ser | Val | Pro | Asn | Lys | Ala | Leu | Glu | Leu | Lys | Asn | Glu |      |
| 710 |     |     |     |     | 715 |     |     |     |     | 720 |     |     |     |     | 725 |      |
| caa | aca | ttg | aga | gca | gat | gag | ata | ctc | cca | tca | gaa | tcc | aaa | caa | aag | 2322 |
| Gln | Thr | Leu | Arg | Ala | Asp | Glu | Ile | Leu | Pro | Ser | Glu | Ser | Lys | Gln | Lys |      |
|     |     |     |     | 730 |     |     |     |     | 735 |     |     |     |     | 740 |     |      |
| gac | tat | gaa | gaa | agt | tct | tgg | gat | tct | gag | agt | ctc | tgt | gag | act | gtt | 2370 |
| Asp | Tyr | Glu | Glu | Ser | Ser | Trp | Asp | Ser | Glu | Ser | Leu | Cys | Glu | Thr | Val |      |
|     |     |     |     | 745 |     |     |     | 750 |     |     |     |     | 755 |     |     |      |
| tca | cag | aag | gat | gtg | tgt | tta | ccc | aag | gct | aca | cat | caa | aaa | gaa | ata | 2418 |

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| Ser | Gln  | Lys | Asp  | Val | Cys | Leu  | Pro  | Lys | Ala  | Thr | His  | Gln  | Lys | Glu  | Ile  |      |
|-----|------|-----|------|-----|-----|------|------|-----|------|-----|------|------|-----|------|------|------|
|     | 760  |     |      |     |     |      | 765  |     |      |     |      | 770  |     |      |      |      |
| gat | aaa  | ata | aat  | gga | aaa | tta  | gaa  | gag | tct  | cct | gat  | aat  | gat | ggt  | ttt  | 2466 |
| Asp | Lys  | Ile | Asn  | Gly | Lys | Leu  | Glu  | Glu | Ser  | Pro | Asp  | Asn  | Asp | Gly  | Phe  |      |
|     | 775  |     |      |     |     | 780  |      |     |      |     | 785  |      |     |      |      |      |
| ctg | aag  | gct | ccc  | tgc | aga | atg  | aaa  | gtt | tct  | att | cca  | act  | aaa | gcc  | tta  | 2514 |
| Leu | Lys  | Ala | Pro  | Cys | Arg | Met  | Lys  | Val | Ser  | Ile | Pro  | Thr  | Lys | Ala  | Leu  |      |
|     | 790  |     |      |     | 795 |      |      |     |      | 800 |      |      |     |      | 805  |      |
| gaa | ttg  | atg | gac  | atg | caa | act  | ttc  | aaa | gca  | gag | cct  | ccc  | gag | aag  | cca  | 2562 |
| Glu | Leu  | Met | Asp  | Met | Gln | Thr  | Phe  | Lys | Ala  | Glu | Pro  | Pro  | Glu | Lys  | Pro  |      |
|     |      |     | 810  |     |     |      |      |     | 815  |     |      |      |     | 820  |      |      |
| tct | gcc  | ttc | gag  | cct | gcc | att  | gaa  | atg | caa  | aag | tct  | gtt  | cca | aat  | aaa  | 2610 |
| Ser | Ala  | Phe | Glu  | Pro | Ala | Ile  | Glu  | Met | Gln  | Lys | Ser  | Val  | Pro | Asn  | Lys  |      |
|     |      | 825 |      |     |     |      |      | 830 |      |     |      |      |     | 835  |      |      |
| gcc | ttg  | gaa | ttg  | aag | aat | gaa  | caa  | aca | ttg  | aga | gca  | gat  | cag | atg  | ttc  | 2658 |
| Ala | Leu  | Glu | Leu  | Lys | Asn | Glu  | Gln  | Thr | Leu  | Arg | Ala  | Asp  | Gln | Met  | Phe  |      |
|     | 840  |     |      |     |     |      | 845  |     |      |     |      | 850  |     |      |      |      |
| cct | tca  | gaa | tca  | aaa | caa | aag  | aag  | gtt | gaa  | gaa | aat  | tct  | tg  | gat  | tct  | 2706 |
| Pro | Ser  | Glu | Ser  | Lys | Gln | Lys  | Lys  | Val | Glu  | Glu | Asn  | Ser  | Trp | Asp  | Ser  |      |
|     | 855  |     |      |     |     | 860  |      |     |      |     | 865  |      |     |      |      |      |
| gag | agt  | ctc | cgt  | gag | act | gtt  | tca  | cag | aag  | gat | gtg  | tgt  | gta | ccc  | aag  | 2754 |
| Glu | Ser  | Leu | Arg  | Glu | Thr | Val  | Ser  | Gln | Lys  | Asp | Val  | Cys  | Val | Pro  | Lys  |      |
|     | 870  |     |      |     | 875 |      |      |     |      | 880 |      |      |     |      | 885  |      |
| gct | aca  | cat | caa  | aaa | gaa | atg  | gat  | aaa | ata  | agt | gga  | aaa  | tta | gaa  | gat  | 2802 |
| Ala | Thr  | His | Gln  | Lys | Glu | Met  | Asp  | Lys | Ile  | Ser | Gly  | Lys  | Leu | Glu  | Asp  |      |
|     |      |     | 890  |     |     |      |      |     | 895  |     |      |      |     | 900  |      |      |
| tca | act  | agc | cta  | tca | aaa | atc  | ttg  | gat | aca  | gtt | cat  | tct  | tgt | gaa  | aga  | 2850 |
| Ser | Thr  | Ser | Leu  | Ser | Lys | Ile  | Leu  | Asp | Thr  | Val | His  | Ser  | Cys | Glu  | Arg  |      |
|     |      | 905 |      |     |     |      |      | 910 |      |     |      |      |     | 915  |      |      |
| gca | agg  | gaa | ctt  | caa | aaa | gat  | cac  | tgt | gaa  | caa | cgt  | aca  | gga | aaa  | atg  | 2898 |
| Ala | Arg  | Glu | Leu  | Gln | Lys | Asp  | His  | Cys | Glu  | Gln | Arg  | Thr  | Gly | Lys  | Met  |      |
|     |      | 920 |      |     |     |      | 925  |     |      |     |      |      | 930 |      |      |      |
| gaa | caa  | atg | aaa  | aag | aag | ttt  | tgt  | gta | ctg  | aaa | aag  | aaa  | ctg | tca  | gaa  | 2946 |
| Glu | Gln  | Met | Lys  | Lys | Lys | Phe  | Cys  | Val | Leu  | Lys | Lys  | Lys  | Leu | Ser  | Glu  |      |
|     | 935  |     |      |     |     | 940  |      |     |      |     | 945  |      |     |      |      |      |
| gca | aaa  | gaa | ata  | aaa | tca | cag  | tta  | gag | aac  | caa | aaa  | gtt  | aaa | tg   | gaa  | 2994 |
| Ala | Lys  | Glu | Ile  | Lys | Ser | Gln  | Leu  | Glu | Asn  | Gln | Lys  | Val  | Lys | Trp  | Glu  |      |
|     | 950  |     |      |     |     | 955  |      |     |      | 960 |      |      |     |      | 965  |      |
| caa | gag  | ctc | tgc  | agt | gtg | aga  | ttg  | act | tta  | aac | caa  | gaa  | gaa | gag  | aag  | 3042 |
| Gln | Glu  | Leu | Cys  | Ser | Val | Arg  | Leu  | Thr | Leu  | Asn | Gln  | Glu  | Glu | Glu  | Lys  |      |
|     |      |     | 970  |     |     |      |      |     | 975  |     |      |      |     |      | 980  |      |
| aga | aga  | aat | gcc  | gat | ata | tta  | aat  | gaa | aaa  | att | agg  | gaa  | gaa | tta  | gga  | 3090 |
| Arg | Arg  | Asn | Ala  | Asp | Ile | Leu  | Asn  | Glu | Lys  | Ile | Arg  | Glu  | Glu | Leu  | Gly  |      |
|     |      | 985 |      |     |     |      |      | 990 |      |     |      |      |     | 995  |      |      |
| aga | atc  | gaa | gag  | cag | cat | agg  | aaa  | gag | tta  | gaa | gtg  | aaa  | caa | caa  | ctt  | 3138 |
| Arg | Ile  | Glu | Glu  | Gln | His | Arg  | Lys  | Glu | Leu  | Glu | Val  | Lys  | Gln | Gln  | Leu  |      |
|     | 1000 |     |      |     |     |      | 1005 |     |      |     |      | 1010 |     |      |      |      |
| gaa | cag  | gct | ctc  | aga | ata | caa  | gat  | ata | gaa  | ttg | aag  | agt  | gta | gaa  | agt  | 3186 |
| Glu | Gln  | Ala | Leu  | Arg | Ile | Gln  | Asp  | Ile | Glu  | Leu | Lys  | Ser  | Val | Glu  | Ser  |      |
|     | 1015 |     |      |     |     | 1020 |      |     |      |     | 1025 |      |     |      |      |      |
| aat | ttg  | aat | cag  | gtt | tct | cac  | act  | cat | gaa  | aat | gaa  | aat  | tat | ctc  | tta  | 3234 |
| Asn | Leu  | Asn | Gln  | Val | Ser | His  | Thr  | His | Glu  | Asn | Glu  | Asn  | Tyr | Leu  | Leu  |      |
|     | 1030 |     |      |     |     | 1035 |      |     |      |     | 1040 |      |     |      | 1045 |      |
| cat | gaa  | aat | tgc  | atg | ttg | aaa  | aag  | gaa | att  | gcc | atg  | cta  | aaa | ctg  | gaa  | 3282 |
| His | Glu  | Asn | Cys  | Met | Leu | Lys  | Lys  | Glu | Ile  | Ala | Met  | Leu  | Lys | Leu  | Glu  |      |
|     |      |     | 1050 |     |     |      |      |     | 1055 |     |      |      |     | 1060 |      |      |
| ata | gcc  | aca | ctg  | aaa | cac | caa  | tac  | cag | gaa  | aag | gaa  | aat  | aaa | tac  | ttt  | 3330 |

| Ile      | Ala  | Thr     | Leu   | Lys      | His   | Gln     | Tyr  | Gln     | Glu        | Lys        | Glu   | Asn  | Lys  | Tyr  | Phe  |      |
|----------|------|---------|-------|----------|-------|---------|------|---------|------------|------------|-------|------|------|------|------|------|
|          |      |         | 1065  |          |       |         |      |         | 1070       |            |       |      | 1075 |      |      |      |
| gag      | gac  | att     | aag   | att      | tta   | aaa     | gaa  | aag     | aat        | gct        | gaa   | ctt  | cag  | atg  | acc  | 3378 |
| Glu      | Asp  | Ile     | Lys   | Ile      | Leu   | Lys     | Glu  | Lys     | Asn        | Ala        | Glu   | Leu  | Gln  | Met  | Thr  |      |
|          |      |         | 1080  |          |       |         | 1085 |         |            |            |       | 1090 |      |      |      |      |
| cta      | aaa  | ctg     | aaa   | gag      | gaa   | tca     | tta  | act     | aaa        | agg        | gca   | tct  | caa  | tat  | agt  | 3426 |
| Leu      | Lys  | Leu     | Lys   | Glu      | Glu   | Ser     | Leu  | Thr     | Lys        | Arg        | Ala   | Ser  | Gln  | Tyr  | Ser  |      |
|          |      |         | 1095  |          |       |         | 1100 |         |            |            |       | 1105 |      |      |      |      |
| ggg      | cag  | ctt     | aaa   | gtt      | ctg   | ata     | gct  | gag     | aac        | aca        | atg   | ctc  | act  | tct  | aaa  | 3474 |
| Gly      | Gln  | Leu     | Lys   | Val      | Leu   | Ile     | Ala  | Glu     | Asn        | Thr        | Met   | Leu  | Thr  | Ser  | Lys  |      |
|          |      |         |       |          |       | 1115    |      |         |            |            | 1120  |      |      |      | 1125 |      |
| ttg      | aag  | gaa     | aaa   | caa      | gac   | aaa     | gaa  | ata     | cta        | gag        | gca   | gaa  | att  | gaa  | tca  | 3522 |
| Leu      | Lys  | Glu     | Lys   | Gln      | Asp   | Lys     | Glu  | Ile     | Leu        | Glu        | Ala   | Glu  | Ile  | Glu  | Ser  |      |
|          |      |         |       |          |       | 1130    |      |         |            | 1135       |       |      |      |      | 1140 |      |
| cac      | cat  | cct     | aga   | ctg      | gct   | tct     | gct  | gta     | caa        | gac        | cat   | gat  | caa  | att  | gtg  | 3570 |
| His      | His  | Pro     | Arg   | Leu      | Ala   | Ser     | Ala  | Val     | Gln        | Asp        | His   | Asp  | Gln  | Ile  | Val  |      |
|          |      |         | 1145  |          |       |         |      |         | 1150       |            |       |      | 1155 |      |      |      |
| aca      | tca  | aga     | aaa   | agt      | caa   | gaa     | cct  | gct     | ttc        | cac        | att   | gca  | gga  | gat  | gct  | 3618 |
| Thr      | Ser  | Arg     | Lys   | Ser      | Gln   | Glu     | Pro  | Ala     | Phe        | His        | Ile   | Ala  | Gly  | Asp  | Ala  |      |
|          |      |         | 1160  |          |       |         | 1165 |         |            |            |       | 1170 |      |      |      |      |
| tgt      | ttg  | caa     | aga   | aaa      | atg   | aat     | gtt  | gat     | gtg        | agt        | agt   | acg  | ata  | tat  | aac  | 3666 |
| Cys      | Leu  | Gln     | Arg   | Lys      | Met   | Asn     | Val  | Asp     | Val        | Ser        | Ser   | Thr  | Ile  | Tyr  | Asn  |      |
|          |      |         | 1175  |          |       |         | 1180 |         |            |            |       | 1185 |      |      |      |      |
| aat      | gag  | gtg     | ctc   | cat      | caa   | cca     | ctt  | tct     | gaa        | gct        | caa   | agg  | aaa  | tcc  | aaa  | 3714 |
| Asn      | Glu  | Val     | Leu   | His      | Gln   | Pro     | Leu  | Ser     | Glu        | Ala        | Gln   | Arg  | Lys  | Ser  | Lys  |      |
|          |      |         |       |          |       | 1195    |      |         |            | 1200       |       |      |      |      | 1205 |      |
| agc      | cta  | aaa     | att   | aat      | ctc   | aat     | tat  | gca     | gga        | gat        | gct   | cta  | aga  | gaa  | aat  | 3762 |
| Ser      | Leu  | Lys     | Ile   | Asn      | Leu   | Asn     | Tyr  | Ala     | Gly        | Asp        | Ala   | Leu  | Arg  | Glu  | Asn  |      |
|          |      |         |       |          |       | 1210    |      |         | 1215       |            |       |      |      | 1220 |      |      |
| aca      | ttg  | gtt     | tca   | gaa      | cat   | gca     | caa  | aga     | gac        | caa        | cgt   | gaa  | aca  | cag  | tgt  | 3810 |
| Thr      | Leu  | Val     | Ser   | Glu      | His   | Ala     | Gln  | Arg     | Asp        | Gln        | Arg   | Glu  | Thr  | Gln  | Cys  |      |
|          |      |         |       |          |       | 1225    |      |         | 1230       |            |       |      | 1235 |      |      |      |
| caa      | atg  | aag     | gaa   | gct      | gaa   | cac     | atg  | tat     | caa        | aac        | gaa   | caa  | gat  | aat  | gtg  | 3858 |
| Gln      | Met  | Lys     | Glu   | Ala      | Glu   | His     | Met  | Tyr     | Gln        | Asn        | Glu   | Gln  | Asp  | Asn  | Val  |      |
|          |      |         | 1240  |          |       |         | 1245 |         |            |            |       | 1250 |      |      |      |      |
| aac      | aaa  | cac     | act   | gaa      | cag   | cag     | gag  | tct     | cta        | gat        | cag   | aaa  | tta  | ttt  | caa  | 3906 |
| Asn      | Lys  | His     | Thr   | Glu      | Gln   | Gln     | Glu  | Ser     | Leu        | Asp        | Gln   | Lys  | Leu  | Phe  | Gln  |      |
|          |      |         | 1255  |          |       | 1260    |      |         |            |            | 1265  |      |      |      |      |      |
| cta      | caa  | agc     | aaa   | aat      | atg   | tgg     | ctt  | caa     | cag        | caa        | tta   | gtt  | cat  | gca  | cat  | 3954 |
| Leu      | Gln  | Ser     | Lys   | Asn      | Met   | Trp     | Leu  | Gln     | Gln        | Gln        | Leu   | Val  | His  | Ala  | His  |      |
|          |      |         |       |          |       | 1275    |      |         |            | 1280       |       |      |      |      | 1285 |      |
| aag      | aaa  | gct     | gac   | aac      | aaa   | agc     | aag  | ata     | aca        | att        | gat   | att  | cat  | ttt  | ctt  | 4002 |
| Lys      | Lys  | Ala     | Asp   | Asn      | Lys   | Ser     | Lys  | Ile     | Thr        | Ile        | Asp   | Ile  | His  | Phe  | Leu  |      |
|          |      |         |       |          | 1290  |         |      |         | 1295       |            |       |      |      | 1300 |      |      |
| gag      | agg  | aaa     | atg   | caa      | cat   | cat     | ctc  | cta     | aaa        | gag        | aaa   | aat  | gag  | gag  | ata  | 4050 |
| Glu      | Arg  | Lys     | Met   | Gln      | His   | His     | Leu  | Leu     | Lys        | Glu        | Lys   | Asn  | Glu  | Glu  | Ile  |      |
|          |      |         | 1305  |          |       |         | 1310 |         |            |            |       |      | 1315 |      |      |      |
| ttt      | aat  | tac     | aat   | aac      | cat   | tta     | aaa  | aac     | cgt        | ata        | tat   | caa  | tat  | gaa  | aaa  | 4098 |
| Phe      | Asn  | Tyr     | Asn   | Asn      | His   | Leu     | Lys  | Asn     | Arg        | Ile        | Tyr   | Gln  | Tyr  | Glu  | Lys  |      |
|          |      |         | 1320  |          |       |         | 1325 |         |            |            |       | 1330 |      |      |      |      |
| gag      | aaa  | gca     | gaa   | aca      | gaa   | aac     | tca  | tga     | gagacaagca | gtaagaaact |       |      |      |      |      | 4145 |
| Glu      | Lys  | Ala     | Glu   | Thr      | Glu   | Asn     | Ser  | *       |            |            |       |      |      |      |      |      |
|          |      |         | 1335  |          |       | 1340    |      |         |            |            |       |      |      |      |      |      |
| tccttttg | gag  | aaacaac | agaca | ccagat   | ctttt | actcaca | act  | catgct  | agga       | ggccag     | tcct  |      |      |      |      | 4205 |
| agcatc   | aact | tatgtt  | gaaa  | atcttacc | aa    | tagtct  | gtgt | caacaga | aata       | cttatt     | tttag |      |      |      |      | 4265 |
| aagaaaa  | aatt | catgatt | ttct  | tcttga   | agcc  | tacagac | ata  | aaataa  | cagt       | gtgaaga    | aatt  |      |      |      |      | 4325 |

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acttggtcac gaattgcata aagctgcaca ggattcccat ctaccctgat gatgcagcag 4385
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tccacctcgg aaa 4458

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Lys Arg Thr Ala Leu His Trp Ala Cys Val Asn Gly His Glu Glu Val
20     25     30
Val Thr Phe Leu Val Asp Arg Lys Cys Gln Leu Asp Val Leu Asp Gly
35     40     45
Glu His Arg Thr Pro Leu Met Lys Ala Leu Gln Cys His Gln Glu Ala
50     55     60
Cys Ala Asn Ile Leu Ile Asp Ser Gly Ala Asp Ile Asn Leu Val Asp
65     70     75     80
Val Tyr Gly Asn Met Ala Leu His Tyr Ala Val Tyr Ser Glu Ile Leu
85     90     95
Ser Val Val Ala Lys Leu Leu Ser His Gly Ala Val Ile Glu Val His
100    105    110
Asn Lys Ala Ser Leu Thr Pro Leu Leu Leu Ser Ile Thr Lys Arg Ser
115    120    125
Glu Gln Ile Val Glu Phe Leu Leu Ile Lys Asn Ala Asn Ala Asn Ala
130    135    140
Val Asn Lys Tyr Lys Cys Thr Ala Leu Met Leu Ala Val Cys His Gly
145    150    155    160
Ser Ser Glu Ile Val Gly Met Leu Leu Gln Gln Asn Val Asp Val Phe
165    170    175
Ala Ala Asp Ile Cys Gly Val Thr Ala Glu His Tyr Ala Val Thr Cys
180    185    190
Gly Phe His His Ile His Glu Gln Ile Met Glu Tyr Ile Arg Lys Leu
195    200    205
Ser Lys Asn His Gln Asn Thr Asn Pro Glu Gly Thr Ser Ala Gly Thr
210    215    220
Pro Asp Glu Ala Ala Pro Leu Ala Glu Arg Thr Pro Asp Thr Ala Glu
225    230    235    240
Ser Leu Val Glu Lys Thr Pro Asp Glu Ala Ala Pro Leu Val Glu Arg
245    250    255
Thr Pro Asp Thr Ala Glu Ser Leu Val Glu Lys Thr Pro Asp Glu Ala
260    265    270
Ala Ser Leu Val Glu Gly Thr Ser Asp Lys Ile Gln Cys Leu Glu Lys
275    280    285
Ala Thr Ser Gly Lys Phe Glu Gln Ser Ala Glu Glu Thr Pro Arg Glu
290    295    300
Ile Thr Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Pro Ala
305    310    315    320
Lys Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Asp Thr Pro

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| 325 |     |     |     |     |     |     |     | 330 |     |     |     |     | 335 |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Arg | Glu | Ile | Met | Ser | Pro | Ala | Lys | Glu | Thr | Ser | Glu | Lys | Phe | Thr | Trp |  |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     | 350 |     |     |     |  |
| Ala | Ala | Lys | Gly | Arg | Pro | Arg | Lys | Ile | Ala | Trp | Glu | Lys | Lys | Glu | Thr |  |
|     |     |     | 355 |     |     |     | 360 |     |     |     | 365 |     |     |     |     |  |
| Pro | Val | Lys | Thr | Gly | Cys | Val | Ala | Arg | Val | Thr | Ser | Asn | Lys | Thr | Lys |  |
|     |     |     | 370 |     |     |     | 375 |     |     |     | 380 |     |     |     |     |  |
| Val | Leu | Glu | Lys | Gly | Arg | Ser | Lys | Met | Ile | Ala | Cys | Pro | Thr | Lys | Glu |  |
| 385 |     |     |     |     |     |     | 390 |     |     |     | 395 |     |     | 400 |     |  |
| Ser | Ser | Thr | Lys | Ala | Ser | Ala | Asn | Asp | Gln | Arg | Phe | Pro | Ser | Glu | Ser |  |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     | 415 |     |     |     |  |
| Lys | Gln | Glu | Glu | Asp | Glu | Glu | Tyr | Ser | Cys | Asp | Ser | Arg | Ser | Leu | Phe |  |
|     |     |     | 420 |     |     |     |     |     | 425 |     |     | 430 |     |     |     |  |
| Glu | Ser | Ser | Ala | Lys | Ile | Gln | Val | Cys | Ile | Pro | Glu | Ser | Ile | Tyr | Gln |  |
|     |     |     | 435 |     |     |     |     |     | 440 |     |     | 445 |     |     |     |  |
| Lys | Val | Met | Glu | Ile | Asn | Arg | Glu | Val | Glu | Glu | Pro | Pro | Lys | Lys | Pro |  |
|     |     |     | 450 |     |     | 455 |     |     |     |     |     | 460 |     |     |     |  |
| Ser | Ala | Phe | Lys | Pro | Ala | Ile | Glu | Met | Gln | Asn | Ser | Val | Pro | Asn | Lys |  |
| 465 |     |     |     |     |     |     | 470 |     |     |     | 475 |     |     | 480 |     |  |
| Ala | Phe | Glu | Leu | Lys | Asn | Glu | Gln | Thr | Leu | Arg | Ala | Asp | Pro | Met | Phe |  |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     | 495 |     |     |     |  |
| Pro | Pro | Glu | Ser | Lys | Gln | Lys | Asp | Tyr | Glu | Glu | Asn | Ser | Trp | Asp | Ser |  |
|     |     |     | 500 |     |     |     |     |     | 505 |     |     | 510 |     |     |     |  |
| Glu | Ser | Leu | Cys | Glu | Thr | Val | Ser | Gln | Lys | Asp | Val | Cys | Leu | Pro | Lys |  |
|     |     |     | 515 |     |     |     |     |     | 520 |     |     | 525 |     |     |     |  |
| Ala | Thr | His | Gln | Lys | Glu | Ile | Asp | Lys | Ile | Asn | Gly | Lys | Leu | Glu | Glu |  |
|     |     |     | 530 |     |     | 535 |     |     |     |     |     | 540 |     |     |     |  |
| Ser | Pro | Asn | Lys | Asp | Gly | Leu | Leu | Lys | Ala | Thr | Cys | Gly | Met | Lys | Val |  |
| 545 |     |     |     | 550 |     |     |     |     |     | 555 |     |     | 560 |     |     |  |
| Ser | Ile | Pro | Thr | Lys | Ala | Leu | Glu | Leu | Lys | Asp | Met | Gln | Thr | Phe | Lys |  |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     | 575 |     |     |     |  |
| Ala | Glu | Pro | Pro | Gly | Lys | Pro | Ser | Ala | Phe | Glu | Pro | Ala | Thr | Glu | Met |  |
|     |     |     | 580 |     |     |     |     |     | 585 |     |     | 590 |     |     |     |  |
| Gln | Lys | Ser | Val | Pro | Asn | Lys | Ala | Leu | Glu | Leu | Lys | Asn | Glu | Gln | Thr |  |
|     |     |     | 595 |     |     | 600 |     |     |     |     |     | 605 |     |     |     |  |
| Trp | Arg | Ala | Asp | Glu | Ile | Leu | Pro | Ser | Glu | Ser | Lys | Gln | Lys | Asp | Tyr |  |
|     |     |     | 610 |     |     | 615 |     |     |     |     |     | 620 |     |     |     |  |
| Glu | Glu | Asn | Ser | Trp | Asp | Thr | Glu | Ser | Leu | Cys | Glu | Thr | Val | Ser | Gln |  |
| 625 |     |     |     | 630 |     |     |     |     |     | 635 |     |     | 640 |     |     |  |
| Lys | Asp | Val | Cys | Leu | Pro | Lys | Ala | Ala | His | Gln | Lys | Glu | Ile | Asp | Lys |  |
|     |     |     | 645 |     |     |     |     |     | 650 |     |     | 655 |     |     |     |  |
| Ile | Asn | Gly | Lys | Leu | Glu | Gly | Ser | Pro | Val | Lys | Asp | Gly | Leu | Leu | Lys |  |
|     |     |     | 660 |     |     | 665 |     |     |     |     |     | 670 |     |     |     |  |
| Ala | Asn | Cys | Gly | Met | Lys | Val | Ser | Ile | Pro | Thr | Lys | Ala | Leu | Glu | Leu |  |
|     |     |     | 675 |     |     | 680 |     |     |     |     |     | 685 |     |     |     |  |
| Met | Asp | Met | Gln | Thr | Phe | Lys | Ala | Glu | Pro | Pro | Glu | Lys | Pro | Ser | Ala |  |
|     |     |     | 690 |     |     | 695 |     |     |     |     |     | 700 |     |     |     |  |
| Phe | Glu | Pro | Ala | Ile | Glu | Met | Gln | Lys | Ser | Val | Pro | Asn | Lys | Ala | Leu |  |
| 705 |     |     |     | 710 |     |     |     |     |     | 715 |     |     | 720 |     |     |  |
| Glu | Leu | Lys | Asn | Glu | Gln | Thr | Leu | Arg | Ala | Asp | Glu | Ile | Leu | Pro | Ser |  |
|     |     |     | 725 |     |     |     |     |     | 730 |     |     | 735 |     |     |     |  |

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|      |      |      |      |     |      |      |     |      |      |      |      |      |      |      |      |  |  |
|------|------|------|------|-----|------|------|-----|------|------|------|------|------|------|------|------|--|--|
| Glu  | Ser  | Lys  | Gln  | Lys | Asp  | Tyr  | Glu | Glu  | Ser  | Ser  | Trp  | Asp  | Ser  | Glu  | Ser  |  |  |
|      |      |      | 740  |     |      |      |     | 745  |      |      |      |      | 750  |      |      |  |  |
| Leu  | Cys  | Glu  | Thr  | Val | Ser  | Gln  | Lys | Asp  | Val  | Cys  | Leu  | Pro  | Lys  | Ala  | Thr  |  |  |
|      |      | 755  |      |     |      |      | 760 |      |      |      |      | 765  |      |      |      |  |  |
| His  | Gln  | Lys  | Glu  | Ile | Asp  | Lys  | Ile | Asn  | Gly  | Lys  | Leu  | Glu  | Glu  | Ser  | Pro  |  |  |
|      | 770  |      |      |     |      | 775  |     |      |      |      | 780  |      |      |      |      |  |  |
| Asp  | Asn  | Asp  | Gly  | Phe | Leu  | Lys  | Ala | Pro  | Cys  | Arg  | Met  | Lys  | Val  | Ser  | Ile  |  |  |
| 785  |      |      |      |     | 790  |      |     |      |      | 795  |      |      |      |      | 800  |  |  |
| Pro  | Thr  | Lys  | Ala  | Leu | Glu  | Leu  | Met | Asp  | Met  | Gln  | Thr  | Phe  | Lys  | Ala  | Glu  |  |  |
|      |      |      | 805  |     |      |      |     |      | 810  |      |      |      |      |      | 815  |  |  |
| Pro  | Pro  | Glu  | Lys  | Pro | Ser  | Ala  | Phe | Glu  | Pro  | Ala  | Ile  | Glu  | Met  | Gln  | Lys  |  |  |
|      |      | 820  |      |     |      |      |     | 825  |      |      |      |      | 830  |      |      |  |  |
| Ser  | Val  | Pro  | Asn  | Lys | Ala  | Leu  | Glu | Leu  | Lys  | Asn  | Glu  | Gln  | Thr  | Leu  | Arg  |  |  |
|      | 835  |      |      |     |      | 840  |     |      |      |      |      | 845  |      |      |      |  |  |
| Ala  | Asp  | Gln  | Met  | Phe | Pro  | Ser  | Glu | Ser  | Lys  | Gln  | Lys  | Lys  | Val  | Glu  | Glu  |  |  |
|      | 850  |      |      |     |      | 855  |     |      |      |      | 860  |      |      |      |      |  |  |
| Asn  | Ser  | Trp  | Asp  | Ser | Glu  | Ser  | Leu | Arg  | Glu  | Thr  | Val  | Ser  | Gln  | Lys  | Asp  |  |  |
| 865  |      |      |      |     | 870  |      |     |      |      | 875  |      |      |      |      | 880  |  |  |
| Val  | Cys  | Val  | Pro  | Lys | Ala  | Thr  | His | Gln  | Lys  | Glu  | Met  | Asp  | Lys  | Ile  | Ser  |  |  |
|      |      |      | 885  |     |      |      |     |      | 890  |      |      |      |      | 895  |      |  |  |
| Gly  | Lys  | Leu  | Glu  | Asp | Ser  | Thr  | Ser | Leu  | Ser  | Lys  | Ile  | Leu  | Asp  | Thr  | Val  |  |  |
|      |      | 900  |      |     |      |      |     | 905  |      |      |      |      | 910  |      |      |  |  |
| His  | Ser  | Cys  | Glu  | Arg | Ala  | Arg  | Glu | Leu  | Gln  | Lys  | Asp  | His  | Cys  | Glu  | Gln  |  |  |
|      | 915  |      |      |     |      |      | 920 |      |      |      |      | 925  |      |      |      |  |  |
| Arg  | Thr  | Gly  | Lys  | Met | Glu  | Gln  | Met | Lys  | Lys  | Lys  | Phe  | Cys  | Val  | Leu  | Lys  |  |  |
|      | 930  |      |      |     |      | 935  |     |      |      |      | 940  |      |      |      |      |  |  |
| Lys  | Lys  | Leu  | Ser  | Glu | Ala  | Lys  | Glu | Ile  | Lys  | Ser  | Gln  | Leu  | Glu  | Asn  | Gln  |  |  |
| 945  |      |      |      |     | 950  |      |     |      |      | 955  |      |      |      |      | 960  |  |  |
| Lys  | Val  | Lys  | Trp  | Glu | Gln  | Glu  | Leu | Cys  | Ser  | Val  | Arg  | Leu  | Thr  | Leu  | Asn  |  |  |
|      |      | 965  |      |     |      |      |     |      | 970  |      |      |      |      | 975  |      |  |  |
| Gln  | Glu  | Glu  | Glu  | Lys | Arg  | Arg  | Asn | Ala  | Asp  | Ile  | Leu  | Asn  | Glu  | Lys  | Ile  |  |  |
|      |      | 980  |      |     |      |      | 985 |      |      |      |      |      | 990  |      |      |  |  |
| Arg  | Glu  | Glu  | Leu  | Gly | Arg  | Ile  | Glu | Glu  | Gln  | His  | Arg  | Lys  | Glu  | Leu  | Glu  |  |  |
|      | 995  |      |      |     |      | 1000 |     |      |      |      |      | 1005 |      |      |      |  |  |
| Val  | Lys  | Gln  | Gln  | Leu | Glu  | Gln  | Ala | Leu  | Arg  | Ile  | Gln  | Asp  | Ile  | Glu  | Leu  |  |  |
|      | 1010 |      |      |     |      | 1015 |     |      |      |      | 1020 |      |      |      |      |  |  |
| Lys  | Ser  | Val  | Glu  | Ser | Asn  | Leu  | Asn | Gln  | Val  | Ser  | His  | Thr  | His  | Glu  | Asn  |  |  |
| 1025 |      |      |      |     | 1030 |      |     |      |      | 1035 |      |      |      |      | 1040 |  |  |
| Glu  | Asn  | Tyr  | Leu  | Leu | His  | Glu  | Asn | Cys  | Met  | Leu  | Lys  | Lys  | Glu  | Ile  | Ala  |  |  |
|      |      |      | 1045 |     |      |      |     |      | 1050 |      |      |      |      | 1055 |      |  |  |
| Met  | Leu  | Lys  | Leu  | Glu | Ile  | Ala  | Thr | Leu  | Lys  | His  | Gln  | Tyr  | Gln  | Glu  | Lys  |  |  |
|      |      | 1060 |      |     |      |      |     | 1065 |      |      |      |      | 1070 |      |      |  |  |
| Glu  | Asn  | Lys  | Tyr  | Phe | Glu  | Asp  | Ile | Lys  | Ile  | Leu  | Lys  | Glu  | Lys  | Asn  | Ala  |  |  |
|      | 1075 |      |      |     |      | 1080 |     |      |      |      |      | 1085 |      |      |      |  |  |
| Glu  | Leu  | Gln  | Met  | Thr | Leu  | Lys  | Leu | Lys  | Glu  | Glu  | Ser  | Leu  | Thr  | Lys  | Arg  |  |  |
|      | 1090 |      |      |     |      | 1095 |     |      |      |      |      | 1100 |      |      |      |  |  |
| Ala  | Ser  | Gln  | Tyr  | Ser | Gly  | Gln  | Leu | Lys  | Val  | Leu  | Ile  | Ala  | Glu  | Asn  | Thr  |  |  |
| 1105 |      |      |      |     | 1110 |      |     |      |      | 1115 |      |      |      |      | 1120 |  |  |
| Met  | Leu  | Thr  | Ser  | Lys | Leu  | Lys  | Glu | Lys  | Gln  | Asp  | Lys  | Glu  | Ile  | Leu  | Glu  |  |  |
|      |      |      | 1125 |     |      |      |     |      | 1130 |      |      |      |      | 1135 |      |  |  |

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Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp  
1140 1145 1150

His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His  
1155 1160 1165

Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser  
1170 1175 1180

Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala  
1185 1190 1195 1200

Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp  
1205 1210 1215

Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln  
1220 1225 1230

Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn  
1235 1240 1245

Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp  
1250 1255 1260

Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln  
1265 1270 1275 1280

Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile  
1285 1290 1295

Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu  
1300 1305 1310

Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile  
1315 1320 1325

Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Asn Ser  
1330 1335 1340

&lt;210&gt; SEQ ID NO 35

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&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: human

&lt;220&gt; FEATURE:

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&lt;222&gt; LOCATION: (12) ... (2522)

&lt;400&gt; SEQUENCE: 35

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agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg      50
      Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu
      1              5              10

ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg      98
Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu
      15              20              25

gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc     146
Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala
      30              35              40              45

ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag     194
Leu Gln Gln Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys
      50              55              60

aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat     242
Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr
      65              70              75

gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca     290
Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro
      80              85              90

gca gtt ttg ccc att gac cat gtt tat ggc act ctg ggc atc gtg gga     338
Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly

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| 95                                                              | 100 | 105 |      |
|-----------------------------------------------------------------|-----|-----|------|
| gcc acc aca acg cag cgc tat tct gac gcc tca aaa ctg agg gag gag |     |     | 386  |
| Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu |     |     |      |
| 110                                                             | 115 | 120 | 125  |
| atc gag gga aag gga tcc ttc act tac ttt gca cag agt aat gag gct |     |     | 434  |
| Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala |     |     |      |
|                                                                 | 130 | 135 | 140  |
| tgg gac aac ttg gat tct gat atc cgt aga ggt ttg gag agc aac gtg |     |     | 482  |
| Trp Asp Asn Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val |     |     |      |
|                                                                 | 145 | 150 | 155  |
| aat gtt gaa tta ctg aat gct tta cat agt cac atg att aat aag aga |     |     | 530  |
| Asn Val Glu Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg |     |     |      |
|                                                                 | 160 | 165 | 170  |
| atg ttg acc aag gac tta aaa aat ggc atg att att cct tca atg tat |     |     | 578  |
| Met Leu Thr Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr |     |     |      |
|                                                                 | 175 | 180 | 185  |
| aac aat ttg ggg ctt ttc att aac cat tat cct aat ggg gtt gtc act |     |     | 626  |
| Asn Asn Leu Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr |     |     |      |
|                                                                 | 190 | 195 | 200  |
| gtt aat tgt gct cga atc atc cat ggg aac cag att gca aca aat ggt |     |     | 674  |
| Val Asn Cys Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly |     |     |      |
|                                                                 | 210 | 215 | 220  |
| gtt gtc cat gtc att gac cgt gtg ctt aca caa att ggt acc tca att |     |     | 722  |
| Val Val His Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile |     |     |      |
|                                                                 | 225 | 230 | 235  |
| caa gac ttc att gaa gca gaa gat gac ctt tca tct ttt aga gca gct |     |     | 770  |
| Gln Asp Phe Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala |     |     |      |
|                                                                 | 240 | 245 | 250  |
| gcc atc aca tcg gac ata ttg gag gcc ctt gga aga gac ggt cac ttc |     |     | 818  |
| Ala Ile Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe |     |     |      |
|                                                                 | 255 | 260 | 265  |
| aca ctc ttt gct ccc acc aat gag gct ttt gag aaa ctt cca cga ggt |     |     | 866  |
| Thr Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly |     |     |      |
|                                                                 | 270 | 275 | 280  |
| gtc cta gaa agg atc atg gga gac aaa gtg gct tcc gaa gct ctt atg |     |     | 914  |
| Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met |     |     |      |
|                                                                 | 290 | 295 | 300  |
| aag tac cac atc tta aat act ctc cag tgt tct gag tct att atg gga |     |     | 962  |
| Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly |     |     |      |
|                                                                 | 305 | 310 | 315  |
| gga gca gtc ttt gag acg ctg gaa gga aat aca att gag ata gga tgt |     |     | 1010 |
| Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys |     |     |      |
|                                                                 | 320 | 325 | 330  |
| gac ggt gac agt ata aca gta aat gga atc aaa atg gtg aac aaa aag |     |     | 1058 |
| Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys |     |     |      |
|                                                                 | 335 | 340 | 345  |
| gat att gtg aca aat aat ggt gtg atc cat ttg att gat cag gtc cta |     |     | 1106 |
| Asp Ile Val Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu |     |     |      |
|                                                                 | 350 | 355 | 360  |
| att cct gat tct gcc aaa caa gtt att gag ctg gct gga aaa cag caa |     |     | 1154 |
| Ile Pro Asp Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln |     |     |      |
|                                                                 | 370 | 375 | 380  |
| acc acc ttc acg gat ctt gtg gcc caa tta ggc ttg gca tct gct ctg |     |     | 1202 |
| Thr Thr Phe Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu |     |     |      |
|                                                                 | 385 | 390 | 395  |
| agg cca gat gga gaa tac act ttg ctg gca cct gtg aat aat gca ttt |     |     | 1250 |
| Arg Pro Asp Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe |     |     |      |

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| 400                                                             | 405 | 410 |      |
|-----------------------------------------------------------------|-----|-----|------|
| tct gat gat act ctc agc atg gat cag cgc ctc ctt aaa tta att ctg |     |     | 1298 |
| Ser Asp Asp Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu |     |     |      |
| 415                                                             | 420 | 425 |      |
| cag aat cac ata ttg aaa gta aaa gtt ggc ctt aat gag ctt tac aac |     |     | 1346 |
| Gln Asn His Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn |     |     |      |
| 430                                                             | 435 | 440 | 445  |
| ggg caa ata ctg gaa acc atc gga ggc aaa cag ctc aga gtc ttc gta |     |     | 1394 |
| Gly Gln Ile Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val |     |     |      |
| 450                                                             | 455 | 460 |      |
| tat cgt aca gct gtc tgc att gaa aat tca tgc atg gag aaa ggg agt |     |     | 1442 |
| Tyr Arg Thr Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser |     |     |      |
| 465                                                             | 470 | 475 |      |
| aag caa ggg aga aac ggt gcg att cac ata ttc cgc gag atc atc aag |     |     | 1490 |
| Lys Gln Gly Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys |     |     |      |
| 480                                                             | 485 | 490 |      |
| cca gca gag aaa tcc ctc cat gaa aag tta aaa caa gat aag cgc ttt |     |     | 1538 |
| Pro Ala Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe |     |     |      |
| 495                                                             | 500 | 505 |      |
| agc acc ttc ctc agc cta ctt gaa gct gca gac ttg aaa gag ctc ctg |     |     | 1586 |
| Ser Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu |     |     |      |
| 510                                                             | 515 | 520 | 525  |
| aca caa cct gga gac tgg aca tta ttt gtg cca acc aat gat gct ttt |     |     | 1634 |
| Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe |     |     |      |
| 530                                                             | 535 | 540 |      |
| aag gga atg act agt gaa gaa aaa gaa att ctg ata cgg gac aaa aat |     |     | 1682 |
| Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn |     |     |      |
| 545                                                             | 550 | 555 |      |
| gct ctt caa aac atc att ctt tat cac ctg aca cca gga gtt ttc att |     |     | 1730 |
| Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile |     |     |      |
| 560                                                             | 565 | 570 |      |
| gga aaa gga ttt gaa cct ggt gtt act aac att tta aag acc aca caa |     |     | 1778 |
| Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln |     |     |      |
| 575                                                             | 580 | 585 |      |
| gga agc aaa atc ttt ctg aaa gaa gta aat gat aca ctt ctg gtg aat |     |     | 1826 |
| Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn |     |     |      |
| 590                                                             | 595 | 600 | 605  |
| gaa ttg aaa tca aaa gaa tct gac atc atg aca aca aat ggt gta att |     |     | 1874 |
| Glu Leu Lys Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile |     |     |      |
| 610                                                             | 615 | 620 |      |
| cat gtt gta gat aaa ctc ctc tat cca gca gac aca cct gtt gga aat |     |     | 1922 |
| His Val Val Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn |     |     |      |
| 625                                                             | 630 | 635 |      |
| gat caa ctg ctg gaa ata ctt aat aaa tta atc aaa tac atc caa att |     |     | 1970 |
| Asp Gln Leu Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile |     |     |      |
| 640                                                             | 645 | 650 |      |
| aag ttt gtt cgt ggt agc acc ttc aaa gaa atc ccc gtg act gtc tat |     |     | 2018 |
| Lys Phe Val Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr |     |     |      |
| 655                                                             | 660 | 665 |      |
| aca act aaa att ata acc aaa gtt gtg gaa cca aaa att aaa gtg att |     |     | 2066 |
| Thr Thr Lys Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile |     |     |      |
| 670                                                             | 675 | 680 | 685  |
| gaa ggc agt ctt cag cct att atc aaa act gaa gga ccc aca cta aca |     |     | 2114 |
| Glu Gly Ser Leu Glu Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr |     |     |      |
| 690                                                             | 695 | 700 |      |
| aaa gtc aaa att gaa ggt gaa cct gaa ttc aga ctg att aaa gaa ggt |     |     | 2162 |
| Lys Val Lys Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly |     |     |      |

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<210> SEQ ID NO 36
<211> LENGTH: 836
<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 36
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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | Pro | Phe | Leu | Pro | Met | Phe | Ser | Leu | Leu | Leu | Leu | Ile | Val |     |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     | 15  |     |     |
| Asn | Pro | Ile | Asn | Ala | Asn | Asn | His | Tyr | Asp | Lys | Ile | Leu | Ala | His | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Arg | Ile | Arg | Gly | Arg | Asp | Gln | Gly | Pro | Asn | Val | Cys | Ala | Leu | Gln | Gln |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Ile | Leu | Gly | Thr | Lys | Lys | Lys | Tyr | Phe | Ser | Thr | Cys | Lys | Asn | Trp | Tyr |

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| 50         |            |            |            |            | 55         |            |            |            |            | 60         |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Lys<br>65  | Lys        | Ser        | Ile        | Cys        | Gly<br>70  | Gln        | Lys        | Thr        | Thr        | Val<br>75  | Leu        | Tyr        | Glu        | Cys        | Cys<br>80  |
| Pro        | Gly        | Tyr        | Met        | Arg<br>85  | Met        | Glu        | Gly        | Met        | Lys<br>90  | Gly        | Cys        | Pro        | Ala        | Val<br>95  | Leu        |
| Pro        | Ile        | Asp        | His        | Val<br>100 | Tyr        | Gly        | Thr        | Leu<br>105 | Gly        | Ile        | Val        | Gly        | Ala<br>110 | Thr        | Thr        |
| Thr        | Gln        | Arg        | Tyr        | Ser<br>115 | Asp        | Ala        | Ser<br>120 | Lys        | Leu        | Arg        | Glu        | Glu<br>125 | Ile        | Glu        | Gly        |
| Lys        | Gly<br>130 | Ser        | Phe        | Thr        | Tyr        | Phe<br>135 | Ala        | Pro        | Ser        | Asn        | Glu<br>140 | Ala        | Trp        | Asp        | Asn        |
| Leu<br>145 | Asp        | Ser        | Asp        | Ile        | Arg<br>150 | Arg        | Gly        | Leu        | Glu        | Ser<br>155 | Asn        | Val        | Asn        | Val        | Glu<br>160 |
| Leu        | Leu        | Asn        | Ala        | Leu<br>165 | His        | Ser        | His        | Met        | Ile<br>170 | Asn        | Lys        | Arg        | Met        | Leu<br>175 | Thr        |
| Lys        | Asp        | Leu        | Lys<br>180 | Asn        | Gly        | Met        | Ile        | Ile<br>185 | Pro        | Ser        | Met        | Tyr        | Asn<br>190 | Asn        | Leu        |
| Gly        | Leu        | Phe<br>195 | Ile        | Asn        | His        | Tyr        | Pro<br>200 | Asn        | Gly        | Val        | Val        | Thr<br>205 | Val        | Asn        | Cys        |
| Ala        | Arg<br>210 | Ile        | Ile        | His        | Gly        | Asn<br>215 | Gln        | Ile        | Ala        | Thr        | Asn<br>220 | Gly        | Val        | Val        | His        |
| Val<br>225 | Ile        | Asp        | Arg        | Val        | Leu<br>230 | Thr        | Gln        | Ile        | Gly        | Thr<br>235 | Ser        | Ile        | Gln        | Asp        | Phe<br>240 |
| Ile        | Glu        | Ala        | Glu        | Asp<br>245 | Asp        | Leu        | Ser        | Ser        | Phe<br>250 | Arg        | Ala        | Ala        | Ala        | Ile<br>255 | Thr        |
| Ser        | Asp        | Ile        | Leu<br>260 | Glu        | Ala        | Leu        | Gly        | Arg<br>265 | Asp        | Gly        | His        | Phe        | Thr<br>270 | Leu        | Phe        |
| Ala        | Pro<br>275 | Thr        | Asn        | Glu        | Ala        | Phe        | Glu<br>280 | Lys        | Leu        | Pro        | Arg        | Gly<br>285 | Val        | Leu        | Glu        |
| Arg        | Ile<br>290 | Met        | Gly        | Asp        | Lys        | Val<br>295 | Ala        | Ser        | Glu        | Ala        | Leu<br>300 | Met        | Lys        | Tyr        | His        |
| Ile<br>305 | Leu        | Asn        | Thr        | Leu        | Gln<br>310 | Cys        | Ser        | Glu        | Ser        | Ile<br>315 | Met        | Gly        | Gly        | Ala        | Val<br>320 |
| Phe        | Glu        | Thr        | Leu        | Glu<br>325 | Gly        | Asn        | Thr        | Ile        | Glu<br>330 | Ile        | Gly        | Cys        | Asp        | Gly<br>335 | Asp        |
| Ser        | Ile        | Thr        | Val<br>340 | Asn        | Gly        | Ile        | Lys        | Met<br>345 | Val        | Asn        | Lys        | Lys        | Asp<br>350 | Ile        | Val        |
| Thr        | Asn<br>355 | Asn        | Gly        | Val        | Ile        | His        | Leu<br>360 | Ile        | Asp        | Gln        | Val        | Leu<br>365 | Ile        | Pro        | Asp        |
| Ser        | Ala<br>370 | Lys        | Gln        | Val        | Ile        | Glu<br>375 | Leu        | Ala        | Gly        | Lys        | Gln<br>380 | Gln        | Thr        | Thr        | Phe        |
| Thr<br>385 | Asp        | Leu        | Val        | Ala        | Gln<br>390 | Leu        | Gly        | Leu        | Ala        | Ser<br>395 | Ala        | Leu        | Arg        | Pro        | Asp<br>400 |
| Gly        | Glu        | Tyr        | Thr        | Leu<br>405 | Leu        | Ala        | Pro        | Val        | Asn<br>410 | Asn        | Ala        | Phe        | Ser        | Asp<br>415 | Asp        |
| Thr        | Leu        | Ser        | Met<br>420 | Asp        | Gln        | Arg        | Leu        | Leu<br>425 | Lys        | Leu        | Ile        | Leu        | Gln<br>430 | Asn        | His        |
| Ile        | Leu<br>435 | Lys        | Val        | Lys        | Val        | Gly        | Leu<br>440 | Asn        | Glu        | Leu        | Tyr        | Asn<br>445 | Gly        | Gln        | Ile        |
| Leu<br>450 | Glu        | Thr        | Ile        | Gly        | Gly<br>455 | Lys        | Gln        | Leu        | Arg        | Val        | Phe<br>460 | Val        | Tyr        | Arg        | Thr        |

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|                                                                 |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|-----------------------------------------------------------------|--|--|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|-----|-----|-----|--|--|-----|-----|
| Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
| 465                                                             |  |  |     |     | 470 |     |     |     |     | 475 |     |  |     |     |     |  |  |     | 480 |
| Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  |     |     | 485 |     |     |     | 490 |     |     |  |     |     |     |  |  | 495 |     |
| Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 500 |     |     |     |     | 505 |     |     |     |  |     |     | 510 |  |  |     |     |
| Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 515 |     |     |     | 520 |     |     |     |     |  |     |     | 525 |  |  |     |     |
| Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 530 |     |     |     | 535 |     |     |     |     |  | 540 |     |     |  |  |     |     |
| Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 545 |     |     | 550 |     |     |     | 555 |     |  |     |     |     |  |  |     | 560 |
| Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  |     | 565 |     |     |     |     | 570 |     |     |  |     |     |     |  |  | 575 |     |
| Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 580 |     |     |     |     | 585 |     |     |     |  |     |     |     |  |  | 590 |     |
| Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 595 |     |     |     | 600 |     |     |     |     |  |     | 605 |     |  |  |     |     |
| Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 610 |     |     |     | 615 |     |     |     |     |  | 620 |     |     |  |  |     |     |
| Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 625 |     |     | 630 |     |     |     |     | 635 |  |     |     |     |  |  |     | 640 |
| Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  |     | 645 |     |     |     |     | 650 |     |     |  |     |     |     |  |  | 655 |     |
| Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 660 |     |     |     |     | 665 |     |     |     |  |     |     |     |  |  | 670 |     |
| Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 675 |     |     |     | 680 |     |     |     |     |  |     | 685 |     |  |  |     |     |
| Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 690 |     |     |     | 695 |     |     |     |     |  |     | 700 |     |  |  |     |     |
| Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 705 |     |     | 710 |     |     |     |     | 715 |  |     |     |     |  |  |     | 720 |
| Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  |     | 725 |     |     |     |     | 730 |     |     |  |     |     |     |  |  | 735 |     |
| Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 740 |     |     |     |     | 745 |     |     |     |  |     |     |     |  |  | 750 |     |
| Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 755 |     |     |     | 760 |     |     |     |     |  |     | 765 |     |  |  |     |     |
| Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 770 |     |     |     | 775 |     |     |     |     |  |     | 780 |     |  |  |     |     |
| Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 785 |     |     | 790 |     |     |     |     | 795 |  |     |     |     |  |  |     | 800 |
| Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  |     | 805 |     |     |     |     | 810 |     |     |  |     |     |     |  |  | 815 |     |
| Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  |     | 820 |     |     |     | 825 |     |     |     |  |     |     |     |  |  | 830 |     |
| Gly Arg Ser Gln                                                 |  |  |     |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |
|                                                                 |  |  | 835 |     |     |     |     |     |     |     |     |  |     |     |     |  |  |     |     |

&lt;210&gt; SEQ ID NO 37

&lt;211&gt; LENGTH: 3129

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<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (12) ... (2438)

<400> SEQUENCE: 37

agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg      50
      Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu
      1             5             10

ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg      98
Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu
      15             20             25

gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc     146
Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala
      30             35             40             45

ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag     194
Leu Gln Gln Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys
      50             55             60

aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat     242
Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr
      65             70             75

gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca     290
Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro
      80             85             90

gca gtt ttg ccc att gac cat gtt tat ggc act ctg ggc atc gtg gga     338
Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly
      95             100            105

gcc acc aca acg cag cgc tat tct gac gcc tca aaa ctg agg gag gag     386
Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu
      110            115            120            125

atc gag gga aag gga tcc ttc act tac ttt gca ccg agt aat gag gct     434
Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala
      130            135            140

tgg gac aac ttg gat tct gat atc cgt aga ggt ttg gag agc aac gtg     482
Trp Asp Asn Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val
      145            150            155

aat gtt gaa tta ctg aat gct tta cat agt cac atg att aat aag aga     530
Asn Val Glu Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg
      160            165            170

atg ttg acc aag gac tta aaa aat ggc atg att att cct tca atg tat     578
Met Leu Thr Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr
      175            180            185

aac aat ttg ggg ctt ttc att aac cat tat cct aat ggg gtt gtc act     626
Asn Asn Leu Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr
      190            195            200            205

gtt aat tgt gct cga atc atc cat ggg aac cag att gca aca aat ggt     674
Val Asn Cys Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly
      210            215            220

gtt gtc cat gtc att gac cgt gtg ctt aca caa att ggt acc tca att     722
Val Val His Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile
      225            230            235

caa gac ttc att gaa gca gaa gat gac ctt tca tct ttt aga gca gct     770
Gln Asp Phe Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala
      240            245            250

gcc atc aca tcg gac ata ttg gag gcc ctt gga aga gac ggt cac ttc     818
Ala Ile Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe
      255            260            265

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| aca ctc ttt gct ccc acc aat gag gct ttt gag aaa ctt cca cga ggt | 866  |
| Thr Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly |      |
| 270 275 280 285                                                 |      |
| gtc cta gaa agg atc atg gga gac aaa gtg gct tcc gaa gct ctt atg | 914  |
| Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met |      |
| 290 295 300                                                     |      |
| aag tac cac atc tta aat act ctc cag tgt tct gag tct att atg gga | 962  |
| Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly |      |
| 305 310 315                                                     |      |
| gga gca gtc ttt gag acg ctg gaa gga aat aca att gag ata gga tgt | 1010 |
| Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys |      |
| 320 325 330                                                     |      |
| gac ggt gac agt ata aca gta aat gga atc aaa atg gtg aac aaa aag | 1058 |
| Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys |      |
| 335 340 345                                                     |      |
| gat att gtg aca aat aat ggt gtg atc cat ttg att gat cag gtc cta | 1106 |
| Asp Ile Val Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu |      |
| 350 355 360 365                                                 |      |
| att cct gat tct gcc aaa caa gtt att gag ctg gct gga aaa cag caa | 1154 |
| Ile Pro Asp Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln |      |
| 370 375 380                                                     |      |
| acc acc ttc acg gat ctt gtg gcc caa tta ggc ttg gca tct gct ctg | 1202 |
| Thr Thr Phe Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu |      |
| 385 390 395                                                     |      |
| agg cca gat gga gaa tac act ttg ctg gca cct gtg aat aat gca ttt | 1250 |
| Arg Pro Asp Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe |      |
| 400 405 410                                                     |      |
| tct gat gat act ctc agc atg gat cag cgc ctc ctt aaa tta att ctg | 1298 |
| Ser Asp Asp Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu |      |
| 415 420 425                                                     |      |
| cag aat cac ata ttg aaa gta aaa gtt ggc ctt aat gag ctt tac aac | 1346 |
| Gln Asn His Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn |      |
| 430 435 440 445                                                 |      |
| ggg caa ata ctg gaa acc atc gga ggc aaa cag ctc aga gtc ttc gta | 1394 |
| Gly Gln Ile Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val |      |
| 450 455 460                                                     |      |
| tat cgt aca gct gtc tgc att gaa aat tca tgc atg gag aaa ggg agt | 1442 |
| Tyr Arg Thr Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser |      |
| 465 470 475                                                     |      |
| aag caa ggg aga aac ggt gcg att cac ata ttc cgc gag atc atc aag | 1490 |
| Lys Gln Gly Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys |      |
| 480 485 490                                                     |      |
| cca gca gag aaa tcc ctc cat gaa aag tta aaa caa gat aag cgc ttt | 1538 |
| Pro Ala Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe |      |
| 495 500 505                                                     |      |
| agc acc ttc ctc agc cta ctt gaa gct gca gac ttg aaa gag ctc ctg | 1586 |
| Ser Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu |      |
| 510 515 520 525                                                 |      |
| aca caa cct gga gac tgg aca tta ttt gtg cca acc aat gat gct ttt | 1634 |
| Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe |      |
| 530 535 540                                                     |      |
| aag gga atg act agt gaa gaa aaa gaa att ctg ata cgg gac aaa aat | 1682 |
| Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn |      |
| 545 550 555                                                     |      |
| gct ctt caa aac atc att ctt tat cac ctg aca cca gga gtt ttc att | 1730 |
| Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile |      |
| 560 565 570                                                     |      |

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| gga aaa gga ttt gaa cct ggt gtt act aac att tta aag acc aca caa<br>Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln<br>575 580 585     | 1778 |
| gga agc aaa atc ttt ctg aaa gaa gta aat gat aca ctt ctg gtg aat<br>Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn<br>590 595 600 605 | 1826 |
| gaa ttg aaa tca aaa gaa tct gac atc atg aca aca aat ggt gta att<br>Glu Leu Lys Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile<br>610 615 620     | 1874 |
| cat gtt gta gat aaa ctc ctc tat cca gca gac aca cct gtt gga aat<br>His Val Val Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn<br>625 630 635     | 1922 |
| gat caa ctg ctg gaa ata ctt aat aaa tta atc aaa tac atc caa att<br>Asp Gln Leu Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile<br>640 645 650     | 1970 |
| aag ttt gtt cgt ggt agc acc ttc aaa gaa atc ccc gtg act gtc tat<br>Lys Phe Val Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr<br>655 660 665     | 2018 |
| aca act aaa att ata acc aaa gtt gtg gaa cca aaa att aaa gtg att<br>Thr Thr Lys Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile<br>670 675 680 685 | 2066 |
| gaa ggc agt ctt cag cct att atc aaa act gaa gga ccc aca cta aca<br>Glu Gly Ser Leu Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr<br>690 695 700         | 2114 |
| aaa gtc aaa att gaa ggt gaa cct gaa ttc aga ctg att aaa gaa ggt<br>Lys Val Lys Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly<br>705 710 715     | 2162 |
| gaa aca ata act gaa gtg atc cat gga gag cca att att aaa aaa tac<br>Glu Thr Ile Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr<br>720 725 730     | 2210 |
| acc aaa atc att gat gga gtg cct gtg gaa ata act gaa aaa gag aca<br>Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr<br>735 740 745     | 2258 |
| cga gaa gaa cga atc att aca ggt cct gaa ata aaa tac act agg att<br>Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile<br>750 755 760 765 | 2306 |
| tct act gga ggt gga gaa aca gaa gaa act ctg aag aaa ttg tta caa<br>Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln<br>770 775 780     | 2354 |
| gaa gac aca ccc gtg agg aag ttg caa gcc aac aaa aaa gtt caa gga<br>Glu Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly<br>785 790 795     | 2402 |
| tct aga aga cga tta agg gaa ggt cgt tct cag tga aaatccaaaa<br>Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln *                                           | 2448 |
| 800 805                                                                                                                                               |      |
| accagaaaaa aatgtttata caaccctaag tcaataacct gaccttagaa aattgtgaga                                                                                     | 2508 |
| gccaaagtga cttcaggaac tgaaacatca gcacaaagaa gcaatcatca aataattctg                                                                                     | 2568 |
| aacacaaaatt taatatTTTT ttttctgaat gagaaacatg agggaaattg tggagttagc                                                                                    | 2628 |
| ctcctgtggt aaaggaattg aagaaaatat aacaccttac accctttttc atcttgacat                                                                                     | 2688 |
| taaaagttct ggctaacttt ggaatccatt agagaaaaat ccttgtcacc agattcatta                                                                                     | 2748 |
| caattcaaat cgaagagttg tgaactgtta toccattgaa aagaccgagc cttgtatgta                                                                                     | 2808 |
| tggtatggat acataaaatg caccgcaagcc attatctctc catgggaagc taagttataa                                                                                    | 2868 |
| aaataggtgc ttggtgtaca aaacttttta tatcaaaagg ctttgacat ttctatatga                                                                                      | 2928 |

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gtgggtttac tggtaaatta tgttatTTTT tacaactaat tttgtactct cagaatgttt 2988
gtcatatgct ttttgcaatg catatTTTT aatctcaaac gtttcaataa aaccattttt 3048
cagatataaa gagaattact tcaaattgag taattcagaa aaactcaaga ttttaagttaa 3108
aaagtgggtt ggacttggga a 3129

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<210> SEQ ID NO 38
<211> LENGTH: 808
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 38

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Ile Val
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Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20     25     30
Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35     40     45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50     55     60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65     70     75     80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85     90     95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100    105    110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115    120    125
Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130    135    140
Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145    150    155    160
Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
165    170    175
Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
180    185    190
Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
195    200    205
Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His
210    215    220
Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe
225    230    235    240
Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr
245    250    255
Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe
260    265    270
Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu
275    280    285
Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His
290    295    300
Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val
305    310    315    320

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
| Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys | Asp | Gly | Asp |  |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |  |
| Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys | Asp | Ile | Val |  |  |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |  |
| Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu | Ile | Pro | Asp |  |  |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |  |
| Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln | Thr | Thr | Phe |  |  |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |  |
| Thr | Asp | Leu | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu | Arg | Pro | Asp |  |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     | 400 |     |  |  |
| Gly | Glu | Tyr | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe | Ser | Asp | Asp |  |  |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |  |
| Thr | Leu | Ser | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu | Gln | Asn | His |  |  |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |  |
| Ile | Leu | Lys | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn | Gly | Gln | Ile |  |  |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |  |
| Leu | Glu | Thr | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val | Tyr | Arg | Thr |  |  |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |  |
| Ala | Val | Cys | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser | Lys | Gln | Gly |  |  |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     | 480 |     |  |  |
| Arg | Asn | Gly | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys | Pro | Ala | Glu |  |  |
|     |     |     |     | 485 |     |     |     | 490 |     |     |     |     |     | 495 |     |  |  |
| Lys | Ser | Leu | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe | Ser | Thr | Phe |  |  |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |  |
| Leu | Ser | Leu | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu | Thr | Gln | Pro |  |  |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |  |
| Gly | Asp | Trp | Thr | Leu | Phe | Val | Pro | Thr | Asn | Asp | Ala | Phe | Lys | Gly | Met |  |  |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |  |
| Thr | Ser | Glu | Glu | Lys | Glu | Ile | Leu | Ile | Arg | Asp | Lys | Asn | Ala | Leu | Gln |  |  |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     | 560 |     |  |  |
| Asn | Ile | Ile | Leu | Tyr | His | Leu | Thr | Pro | Gly | Val | Phe | Ile | Gly | Lys | Gly |  |  |
|     |     |     | 565 |     |     |     |     | 570 |     |     |     |     |     | 575 |     |  |  |
| Phe | Glu | Pro | Gly | Val | Thr | Asn | Ile | Leu | Lys | Thr | Thr | Gln | Gly | Ser | Lys |  |  |
|     |     | 580 |     |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |  |
| Ile | Phe | Leu | Lys | Glu | Val | Asn | Asp | Thr | Leu | Leu | Val | Asn | Glu | Leu | Lys |  |  |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |  |
| Ser | Lys | Glu | Ser | Asp | Ile | Met | Thr | Thr | Asn | Gly | Val | Ile | His | Val | Val |  |  |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |  |
| Asp | Lys | Leu | Leu | Tyr | Pro | Ala | Asp | Thr | Pro | Val | Gly | Asn | Asp | Gln | Leu |  |  |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     | 640 |     |  |  |
| Leu | Glu | Ile | Leu | Asn | Lys | Leu | Ile | Lys | Tyr | Ile | Gln | Ile | Lys | Phe | Val |  |  |
|     |     |     | 645 |     |     |     |     | 650 |     |     |     |     |     | 655 |     |  |  |
| Arg | Gly | Ser | Thr | Phe | Lys | Glu | Ile | Pro | Val | Thr | Val | Tyr | Thr | Thr | Lys |  |  |
|     |     | 660 |     |     |     |     |     | 665 |     |     |     |     | 670 |     |     |  |  |
| Ile | Ile | Thr | Lys | Val | Val | Glu | Pro | Lys | Ile | Lys | Val | Ile | Glu | Gly | Ser |  |  |
|     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |  |  |
| Leu | Gln | Pro | Ile | Ile | Lys | Thr | Glu | Gly | Pro | Thr | Leu | Thr | Lys | Val | Lys |  |  |
|     | 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |  |  |
| Ile | Glu | Gly | Glu | Pro | Glu | Phe | Arg | Leu | Ile | Lys | Glu | Gly | Glu | Thr | Ile |  |  |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     | 720 |     |  |  |
| Thr | Glu | Val | Ile | His | Gly | Glu | Pro | Ile | Ile | Lys | Lys | Tyr | Thr | Lys | Ile |  |  |

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| 725                                                              | 730 | 735 |     |
|------------------------------------------------------------------|-----|-----|-----|
| Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu  |     |     |     |
| 740                                                              | 745 | 750 |     |
| Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly  |     |     |     |
| 755                                                              | 760 | 765 |     |
| Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Asp Thr  |     |     |     |
| 770                                                              | 775 | 780 |     |
| Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg  |     |     |     |
| 785                                                              | 790 | 795 | 800 |
| Arg Leu Arg Glu Gly Arg Ser Gln                                  |     |     |     |
| 805                                                              |     |     |     |
| <br><210> SEQ ID NO 39                                           |     |     |     |
| <211> LENGTH: 3132                                               |     |     |     |
| <212> TYPE: DNA                                                  |     |     |     |
| <213> ORGANISM: human                                            |     |     |     |
| <220> FEATURE:                                                   |     |     |     |
| <221> NAME/KEY: CDS                                              |     |     |     |
| <222> LOCATION: (12) ... (2441)                                  |     |     |     |
| <br><400> SEQUENCE: 39                                           |     |     |     |
| agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg |     |     | 50  |
| Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu                  |     |     |     |
| 1 5 10                                                           |     |     |     |
| ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg  |     |     | 98  |
| Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu  |     |     |     |
| 15 20 25                                                         |     |     |     |
| gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc  |     |     | 146 |
| Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala  |     |     |     |
| 30 35 40 45                                                      |     |     |     |
| ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag  |     |     | 194 |
| Leu Gln Gln Ile Leu Gly Thr Lys Lys Tyr Phe Ser Thr Cys Lys      |     |     |     |
| 50 55 60                                                         |     |     |     |
| aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat  |     |     | 242 |
| Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr  |     |     |     |
| 65 70 75                                                         |     |     |     |
| gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca  |     |     | 290 |
| Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro  |     |     |     |
| 80 85 90                                                         |     |     |     |
| gca gtt ttg ccc att gac cat gtt tat ggc act ctg ggc atc gtg gga  |     |     | 338 |
| Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly  |     |     |     |
| 95 100 105                                                       |     |     |     |
| gcc acc aca acg cag cgc tat tct gac gcc tca aaa ctg agg gag gag  |     |     | 386 |
| Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu  |     |     |     |
| 110 115 120 125                                                  |     |     |     |
| atc gag gga aag gga tcc ttc act tac ttt gca cgg agt aat gag gct  |     |     | 434 |
| Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala  |     |     |     |
| 130 135 140                                                      |     |     |     |
| tgg gac aac ttg gat tct gat atc cgt aga ggt ttg gag agc aac gtg  |     |     | 482 |
| Trp Asp Asn Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val  |     |     |     |
| 145 150 155                                                      |     |     |     |
| aat gtt gaa tta ctg aat gct tta cat agt cac atg att aat aag aga  |     |     | 530 |
| Asn Val Glu Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg  |     |     |     |
| 160 165 170                                                      |     |     |     |
| atg ttg acc aag gac tta aaa aat ggc atg att att cct tca atg tat  |     |     | 578 |
| Met Leu Thr Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr  |     |     |     |
| 175 180 185                                                      |     |     |     |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| aac aat ttg ggg ctt ttc att aac cat tat cct aat ggg gtt gtc act | 626  |
| Asn Asn Leu Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr |      |
| 190 195 200 205                                                 |      |
| ggt aat tgt gct cga atc atc cat ggg aac cag att gca aca aat ggt | 674  |
| Val Asn Cys Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly |      |
| 210 215 220                                                     |      |
| ggt gtc cat gtc att gac cgt gtg ctt aca caa att ggt acc tca att | 722  |
| Val Val His Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile |      |
| 225 230 235                                                     |      |
| caa gac ttc att gaa gca gaa gat gac ctt tca tct ttt aga gca gct | 770  |
| Gln Asp Phe Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala |      |
| 240 245 250                                                     |      |
| gcc atc aca tcg gac ata ttg gag gcc ctt gga aga gac ggt cac ttc | 818  |
| Ala Ile Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe |      |
| 255 260 265                                                     |      |
| aca ctc ttt gct ccc acc aat gag gct ttt gag aaa ctt cca cga ggt | 866  |
| Thr Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly |      |
| 270 275 280 285                                                 |      |
| gtc cta gaa agg atc atg gga gac aaa gtg gct tcc gaa gct ctt atg | 914  |
| Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met |      |
| 290 295 300                                                     |      |
| aag tac cac atc tta aat act ctc cag tgt tct gag tct att atg gga | 962  |
| Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly |      |
| 305 310 315                                                     |      |
| gga gca gtc ttt gag acg ctg gaa gga aat aca att gag ata gga tgt | 1010 |
| Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys |      |
| 320 325 330                                                     |      |
| gac ggt gac agt ata aca gta aat gga atc aaa atg gtg aac aaa aag | 1058 |
| Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys |      |
| 335 340 345                                                     |      |
| gat att gtg aca aat aat ggt gtg atc cat ttg att gat cag gtc cta | 1106 |
| Asp Ile Val Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu |      |
| 350 355 360 365                                                 |      |
| att cct gat tct gcc aaa caa gtt att gag ctg gct gga aaa cag caa | 1154 |
| Ile Pro Asp Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln |      |
| 370 375 380                                                     |      |
| acc acc ttc acg gat ctt gtg gcc caa tta ggc ttg gca tct gct ctg | 1202 |
| Thr Thr Phe Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu |      |
| 385 390 395                                                     |      |
| agg cca gat gga gaa tac act ttg ctg gca cct gtg aat aat gca ttt | 1250 |
| Arg Pro Asp Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe |      |
| 400 405 410                                                     |      |
| tct gat gat act ctc agc atg gat cag cgc ctc ctt aaa tta att ctg | 1298 |
| Ser Asp Asp Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu |      |
| 415 420 425                                                     |      |
| cag aat cac ata ttg aaa gta aaa gtt ggc ctt aat gag ctt tac aac | 1346 |
| Gln Asn His Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn |      |
| 430 435 440 445                                                 |      |
| ggg caa ata ctg gaa acc atc gga ggc aaa cag ctc aga gtc ttc gta | 1394 |
| Gly Gln Ile Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val |      |
| 450 455 460                                                     |      |
| tat cgt aca gct gtc tgc att gaa aat tca tgc atg gag aaa ggg agt | 1442 |
| Tyr Arg Thr Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser |      |
| 465 470 475                                                     |      |
| aag caa ggg aga aac ggt gcg att cac ata ttc cgc gag atc atc aag | 1490 |
| Lys Gln Gly Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys |      |
| 480 485 490                                                     |      |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| cca gca gag aaa tcc ctc cat gaa aag tta aaa caa gat aag cgc ttt | 1538 |
| Pro Ala Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe |      |
| 495 500 505                                                     |      |
| agc acc ttc ctc agc cta ctt gaa gct gca gac ttg aaa gag ctc ctg | 1586 |
| Ser Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu |      |
| 510 515 520 525                                                 |      |
| aca caa cct gga gac tgg aca tta ttt gtg cca acc aat gat gct ttt | 1634 |
| Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe |      |
| 530 535 540                                                     |      |
| aag gga atg act agt gaa gaa aaa gaa att ctg ata cgg gac aaa aat | 1682 |
| Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn |      |
| 545 550 555                                                     |      |
| gct ctt caa aac atc att ctt tat cac ctg aca cca gga gtt ttc att | 1730 |
| Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile |      |
| 560 565 570                                                     |      |
| gga aaa gga ttt gaa cct ggt gtt act aac att tta aag acc aca caa | 1778 |
| Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln |      |
| 575 580 585                                                     |      |
| gga agc aaa atc ttt ctg aaa gaa gta aat gat aca ctt ctg gtg aat | 1826 |
| Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn |      |
| 590 595 600 605                                                 |      |
| gaa ttg aaa tca aaa gaa tct gac atc atg aca aca aat ggt gta att | 1874 |
| Glu Leu Lys Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile |      |
| 610 615 620                                                     |      |
| cat gtt gta gat aaa ctc ctc tat cca gca gac aca cct gtt gga aat | 1922 |
| His Val Val Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn |      |
| 625 630 635                                                     |      |
| gat caa ctg ctg gaa ata ctt aat aaa tta atc aaa tac atc caa att | 1970 |
| Asp Gln Leu Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile |      |
| 640 645 650                                                     |      |
| aag ttt gtt cgt ggt agc acc ttc aaa gaa atc ccc gtg act gtc tat | 2018 |
| Lys Phe Val Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr |      |
| 655 660 665                                                     |      |
| aga ccc aca cta aca aaa gtc aaa att gaa ggt gaa cct gaa ttc aga | 2066 |
| Arg Pro Thr Leu Thr Lys Val Lys Ile Glu Gly Glu Pro Glu Phe Arg |      |
| 670 675 680 685                                                 |      |
| ctg att aaa gaa ggt gaa aca ata act gaa gtg atc cat gga gag cca | 2114 |
| Leu Ile Lys Glu Gly Glu Thr Ile Thr Glu Val Ile His Gly Glu Pro |      |
| 690 695 700                                                     |      |
| att att aaa aaa tac acc aaa atc att gat gga gtg cct gtg gaa ata | 2162 |
| Ile Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile |      |
| 705 710 715                                                     |      |
| act gaa aaa gag aca cga gaa gaa cga atc att aca ggt cct gaa ata | 2210 |
| Thr Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile |      |
| 720 725 730                                                     |      |
| aaa tac act agg att tct act gga ggt gga gaa aca gaa gaa act ctg | 2258 |
| Lys Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu |      |
| 735 740 745                                                     |      |
| aag aaa ttg tta caa gaa gag gtc acc aag gtc acc aaa ttc att gaa | 2306 |
| Lys Lys Leu Leu Gln Glu Glu Val Thr Lys Val Thr Lys Phe Ile Glu |      |
| 750 755 760 765                                                 |      |
| ggt ggt gat ggt cat tta ttt gaa gat gaa gaa att aaa aga ctg ctt | 2354 |
| Gly Gly Asp Gly His Leu Phe Glu Asp Glu Glu Ile Lys Arg Leu Leu |      |
| 770 775 780                                                     |      |
| cag gga gac aca ccc gtg agg aag ttg caa gcc aac aaa aaa gtt caa | 2402 |
| Gln Gly Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln |      |
| 785 790 795                                                     |      |

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gga tct aga aga cga tta agg gaa ggt cgt tct cag tga aaatccaaaa 2451
Gly Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln *
      800      805

accagaaaaa aatgtttata caaccctaag tcaataacct gaccttagaa aattgtgaga 2511

gccaaagttga cttcaggaac tgaacatca gcacaaagaa gcaatcatca aataattctg 2571

aacacaaatt taatatTTTT ttttctgaat gagaaacatg agggaaattg tggagttagc 2631

ctcctgtggt aaaggaattg aagaaaatat aacaccttac accctttttc atcttgacat 2691

taaaagttct ggctaacttt ggaatccatt agagaaaaat cctgtgcacc agattcatta 2751

caattcaaat cgaagagttg tgaactgtta tccattgaa aagaccgagc cttgtatgta 2811

tgttatggat acataaaatg cacgcaagcc attatctctc catgggaagc taagttataa 2871

aaataggtgc ttggtgtaca aaacttttta tatcaaaagg ctttgcacat ttctatatga 2931

gtgggtttac tggtaaatta tgttattttt tacaactaat tttgtactct cagaatgttt 2991

gtcatatgct tcttgcaatg catatttttt aatctcaaac gtttcaataa aaccattttt 3051

cagatataaa gagaattact tcaaattgag taattcagaa aaactcaaga ttttaagttaa 3111

aaagtgggtt ggacttggga a 3132

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&lt;210&gt; SEQ ID NO 40

&lt;211&gt; LENGTH: 809

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 40

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val
1           5           10          15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20          25          30

Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35          40          45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50          55          60

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65          70          75          80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85          90          95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100         105         110

Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115         120         125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130         135         140

Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145         150         155         160

Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
165         170         175

Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
180         185         190

Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
195         200         205

Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His

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| 210                                                                                | 215 | 220 |
|------------------------------------------------------------------------------------|-----|-----|
| Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe<br>225 230 235 240 |     |     |
| Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr<br>245 250 255     |     |     |
| Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe<br>260 265 270     |     |     |
| Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu<br>275 280 285     |     |     |
| Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His<br>290 295 300     |     |     |
| Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val<br>305 310 315 320 |     |     |
| Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp<br>325 330 335     |     |     |
| Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val<br>340 345 350     |     |     |
| Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp<br>355 360 365     |     |     |
| Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe<br>370 375 380     |     |     |
| Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp<br>385 390 395 400 |     |     |
| Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp<br>405 410 415     |     |     |
| Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His<br>420 425 430     |     |     |
| Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile<br>435 440 445     |     |     |
| Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr<br>450 455 460     |     |     |
| Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly<br>465 470 475 480 |     |     |
| Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu<br>485 490 495     |     |     |
| Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe<br>500 505 510     |     |     |
| Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro<br>515 520 525     |     |     |
| Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met<br>530 535 540     |     |     |
| Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln<br>545 550 555 560 |     |     |
| Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly<br>565 570 575     |     |     |
| Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys<br>580 585 590     |     |     |
| Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys<br>595 600 605     |     |     |
| Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val<br>610 615 620     |     |     |

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Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu  
 625 630 635 640  
 Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val  
 645 650 655  
 Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Arg Pro Thr  
 660 665 670  
 Leu Thr Lys Val Lys Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys  
 675 680 685  
 Glu Gly Glu Thr Ile Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys  
 690 695 700  
 Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys  
 705 710 715 720  
 Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr  
 725 730 735  
 Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu  
 740 745 750  
 Leu Gln Glu Glu Val Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp  
 755 760 765  
 Gly His Leu Phe Glu Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp  
 770 775 780  
 Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg  
 785 790 795 800  
 Arg Arg Leu Arg Glu Gly Arg Ser Gln  
 805

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 <212> TYPE: DNA  
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 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (12) ... (2357)

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| agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg | 50  |
| Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu                  |     |
| 1 5 10                                                           |     |
| ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg  | 98  |
| Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu  |     |
| 15 20 25                                                         |     |
| gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc  | 146 |
| Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala  |     |
| 30 35 40 45                                                      |     |
| ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag  | 194 |
| Leu Gln Gln Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys  |     |
| 50 55 60                                                         |     |
| aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat  | 242 |
| Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr  |     |
| 65 70 75                                                         |     |
| gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca  | 290 |
| Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro  |     |
| 80 85 90                                                         |     |
| gca gtt ttg ccc att gac cat gtt tat ggc act ctg ggc atc gtg gga  | 338 |
| Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly  |     |
| 95 100 105                                                       |     |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| gcc acc aca acg cag cgc tat tct gac gcc tca aaa ctg agg gag gag | 386  |
| Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu |      |
| 110 115 120 125                                                 |      |
| atc gag gga aag gga tcc ttc act tac ttt gca ccg agt aat gag gct | 434  |
| Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala |      |
| 130 135 140                                                     |      |
| tgg gac aac ttg gat tct gat atc cgt aga ggt ttg gag agc aac gtg | 482  |
| Trp Asp Asn Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val |      |
| 145 150 155                                                     |      |
| aat gtt gaa tta ctg aat gct tta cat agt cac atg att aat aag aga | 530  |
| Asn Val Glu Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg |      |
| 160 165 170                                                     |      |
| atg ttg acc aag gac tta aaa aat ggc atg att att cct tca atg tat | 578  |
| Met Leu Thr Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr |      |
| 175 180 185                                                     |      |
| aac aat ttg ggg ctt ttc att aac cat tat cct aat ggg gtt gtc act | 626  |
| Asn Asn Leu Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr |      |
| 190 195 200 205                                                 |      |
| gtt aat tgt gct cga atc atc cat ggg aac cag att gca aca aat ggt | 674  |
| Val Asn Cys Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly |      |
| 210 215 220                                                     |      |
| gtt gtc cat gtc att gac cgt gtg ctt aca caa att ggt acc tca att | 722  |
| Val Val His Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile |      |
| 225 230 235                                                     |      |
| caa gac ttc att gaa gca gaa gat gac ctt tca tct ttt aga gca gct | 770  |
| Gln Asp Phe Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala |      |
| 240 245 250                                                     |      |
| gcc atc aca tcg gac ata ttg gag gcc ctt gga aga gac ggt cac ttc | 818  |
| Ala Ile Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe |      |
| 255 260 265                                                     |      |
| aca ctc ttt gct ccc acc aat gag gct ttt gag aaa ctt cca cga ggt | 866  |
| Thr Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly |      |
| 270 275 280 285                                                 |      |
| gtc cta gaa agg atc atg gga gac aaa gtg gct tcc gaa gct ctt atg | 914  |
| Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met |      |
| 290 295 300                                                     |      |
| aag tac cac atc tta aat act ctc cag tgt tct gag tct att atg gga | 962  |
| Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly |      |
| 305 310 315                                                     |      |
| gga gca gtc ttt gag acg ctg gaa gga aat aca att gag ata gga tgt | 1010 |
| Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys |      |
| 320 325 330                                                     |      |
| gac ggt gac agt ata aca gta aat gga atc aaa atg gtg aac aaa aag | 1058 |
| Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys |      |
| 335 340 345                                                     |      |
| gat att gtg aca aat aat ggt gtg atc cat ttg att gat cag gtc cta | 1106 |
| Asp Ile Val Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu |      |
| 350 355 360 365                                                 |      |
| att cct gat tct gcc aaa caa gtt att gag ctg gct gga aaa cag caa | 1154 |
| Ile Pro Asp Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln |      |
| 370 375 380                                                     |      |
| acc acc ttc acg gat ctt gtg gcc caa tta ggc ttg gca tct gct ctg | 1202 |
| Thr Thr Phe Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu |      |
| 385 390 395                                                     |      |
| agg cca gat gga gaa tac act ttg ctg gca cct gtg aat aat gca ttt | 1250 |
| Arg Pro Asp Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe |      |
| 400 405 410                                                     |      |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| tct gat gat act ctc agc atg gat cag cgc ctc ctt aaa tta att ctg | 1298 |
| Ser Asp Asp Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu |      |
| 415 420 425                                                     |      |
| cag aat cac ata ttg aaa gta aaa gtt ggc ctt aat gag ctt tac aac | 1346 |
| Gln Asn His Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn |      |
| 430 435 440 445                                                 |      |
| ggg caa ata ctg gaa acc atc gga ggc aaa cag ctc aga gtc ttc gta | 1394 |
| Gly Gln Ile Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val |      |
| 450 455 460                                                     |      |
| tat cgt aca gct gtc tgc att gaa aat tca tgc atg gag aaa ggg agt | 1442 |
| Tyr Arg Thr Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser |      |
| 465 470 475                                                     |      |
| aag caa ggg aga aac ggt gcg att cac ata ttc cgc gag atc atc aag | 1490 |
| Lys Gln Gly Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys |      |
| 480 485 490                                                     |      |
| cca gca gag aaa tcc ctc cat gaa aag tta aaa caa gat aag cgc ttt | 1538 |
| Pro Ala Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe |      |
| 495 500 505                                                     |      |
| agc acc ttc ctc agc cta ctt gaa gct gca gac ttg aaa gag ctc ctg | 1586 |
| Ser Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu |      |
| 510 515 520 525                                                 |      |
| aca caa cct gga gac tgg aca tta ttt gtg cca acc aat gat gct ttt | 1634 |
| Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe |      |
| 530 535 540                                                     |      |
| aag gga atg act agt gaa gaa aaa gaa att ctg ata cgg gac aaa aat | 1682 |
| Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn |      |
| 545 550 555                                                     |      |
| gct ctt caa aac atc att ctt tat cac ctg aca cca gga gtt ttc att | 1730 |
| Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile |      |
| 560 565 570                                                     |      |
| gga aaa gga ttt gaa cct ggt gtt act aac att tta aag acc aca caa | 1778 |
| Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln |      |
| 575 580 585                                                     |      |
| gga agc aaa atc ttt ctg aaa gaa gta aat gat aca ctt ctg gtg aat | 1826 |
| Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn |      |
| 590 595 600 605                                                 |      |
| gaa ttg aaa tca aaa gaa tct gac atc atg aca aca aat ggt gta att | 1874 |
| Glu Leu Lys Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile |      |
| 610 615 620                                                     |      |
| cat gtt gta gat aaa ctc ctc tat cca gca gac aca cct gtt gga aat | 1922 |
| His Val Val Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn |      |
| 625 630 635                                                     |      |
| gat caa ctg ctg gaa ata ctt aat aaa tta atc aaa tac atc caa att | 1970 |
| Asp Gln Leu Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile |      |
| 640 645 650                                                     |      |
| aag ttt gtt cgt ggt agc acc ttc aaa gaa atc ccc gtg act gtc tat | 2018 |
| Lys Phe Val Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr |      |
| 655 660 665                                                     |      |
| aga ccc aca cta aca aaa gtc aaa att gaa ggt gaa cct gaa ttc aga | 2066 |
| Arg Pro Thr Leu Thr Lys Val Lys Ile Glu Gly Glu Pro Glu Phe Arg |      |
| 670 675 680 685                                                 |      |
| ctg att aaa gaa ggt gaa aca ata act gaa gtg atc cat gga gag cca | 2114 |
| Leu Ile Lys Glu Gly Glu Thr Ile Thr Glu Val Ile His Gly Glu Pro |      |
| 690 695 700                                                     |      |
| att att aaa aaa tac acc aaa atc att gat gga gtg cct gtg gaa ata | 2162 |
| Ile Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile |      |
| 705 710 715                                                     |      |

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act gaa aaa gag aca cga gaa gaa cga atc att aca ggt cct gaa ata 2210
Thr Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile
      720              725              730

aaa tac act agg att tct act gga ggt gga gaa aca gaa gaa act ctg 2258
Lys Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu
      735              740              745

aag aaa ttg tta caa gaa gac aca ccc gtg agg aag ttg caa gcc aac 2306
Lys Lys Leu Leu Gln Glu Asp Thr Pro Val Arg Lys Leu Gln Ala Asn
      750              755              760              765

aaa aaa gtt caa ggt tct aga aga cga tta agg gaa ggt cgt tct cag 2354
Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln
      770              775              780

tga aaatccaaaa accagaaaaa aatgtttata caaccctaag tcaataacct 2407
*

gaccttagaa aattgtgaga gccaaagtga cttcaggaac tgaacatca gcacaaagaa 2467

gcaatcatca aataattctg aacacaaatt taatatTTTT tttctgaaat gagaaacatg 2527

agggaaattg tggagttagc ctctgtggt aaaggaattg aagaaaatat aacaccttac 2587

accctTTTTc atcttgacat taaaagtTct ggctaacttt ggaatccatt agagaaaaat 2647

cctgtgcacc agattcatta caattcaaat cgaagagttg tgaactgtta tccattgaa 2707

aagaccgagc cttgtatgta tgttatggat acataaaatg cacgcaagcc attatctctc 2767

catgggaagc taagtataa aaataggtgc ttggtgtaca aaactTTTTa tatcaaagg 2827

cttgcacat ttctatatga gtgggtttac tggtaaatta tgttatTTTT tacaactaat 2887

tttgactctc cagaatgttt gtcatatgct tcttgcaatg catatTTTTt aatctcaaac 2947

gtttcaataa aaccattttt cagatataaa gagaattact tcaaatgag taattcagaa 3007

aaactcaaga tttaagttaa aaagtgttt ggacttgga a 3048

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<210> SEQ ID NO 42
<211> LENGTH: 781
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 42

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Ile Val
1              5              10              15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
      20              25              30

Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
      35              40              45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
      50              55              60

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
      65              70              75              80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
      85              90              95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
      100             105             110

Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
      115             120             125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
      130             135             140

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asp | Ser | Asp | Ile | Arg | Arg | Gly | Leu | Glu | Ser | Asn | Val | Asn | Val | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Leu | Leu | Asn | Ala | Leu | His | Ser | His | Met | Ile | Asn | Lys | Arg | Met | Leu | Thr |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Lys | Asp | Leu | Lys | Asn | Gly | Met | Ile | Ile | Pro | Ser | Met | Tyr | Asn | Asn | Leu |
|     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |     |
| Gly | Leu | Phe | Ile | Asn | His | Tyr | Pro | Asn | Gly | Val | Val | Thr | Val | Asn | Cys |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Ala | Arg | Ile | Ile | His | Gly | Asn | Gln | Ile | Ala | Thr | Asn | Gly | Val | Val | His |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Val | Ile | Asp | Arg | Val | Leu | Thr | Gln | Ile | Gly | Thr | Ser | Ile | Gln | Asp | Phe |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Ile | Glu | Ala | Glu | Asp | Asp | Leu | Ser | Ser | Phe | Arg | Ala | Ala | Ala | Ile | Thr |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Ser | Asp | Ile | Leu | Glu | Ala | Leu | Gly | Arg | Asp | Gly | His | Phe | Thr | Leu | Phe |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ala | Pro | Thr | Asn | Glu | Ala | Phe | Glu | Lys | Leu | Pro | Arg | Gly | Val | Leu | Glu |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Arg | Ile | Met | Gly | Asp | Lys | Val | Ala | Ser | Glu | Ala | Leu | Met | Lys | Tyr | His |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ile | Leu | Asn | Thr | Leu | Gln | Cys | Ser | Glu | Ser | Ile | Met | Gly | Gly | Ala | Val |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys | Asp | Gly | Asp |
|     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys | Asp | Ile | Val |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu | Ile | Pro | Asp |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln | Thr | Thr | Phe |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Thr | Asp | Leu | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu | Arg | Pro | Asp |
| 385 |     |     |     |     | 390 |     |     |     | 395 |     |     |     |     |     | 400 |
| Gly | Glu | Tyr | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe | Ser | Asp | Asp |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Thr | Leu | Ser | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu | Gln | Asn | His |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ile | Leu | Lys | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn | Gly | Gln | Ile |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Leu | Glu | Thr | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val | Tyr | Arg | Thr |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Val | Cys | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser | Lys | Gln | Gly |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Arg | Asn | Gly | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys | Pro | Ala | Glu |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Lys | Ser | Leu | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe | Ser | Thr | Phe |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Leu | Ser | Leu | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu | Thr | Gln | Pro |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Gly | Asp | Trp | Thr | Leu | Phe | Val | Pro | Thr | Asn | Asp | Ala | Phe | Lys | Gly | Met |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Thr | Ser | Glu | Glu | Lys | Glu | Ile | Leu | Ile | Arg | Asp | Lys | Asn | Ala | Leu | Gln |

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| 545                 | 550                         | 555                     | 560 |
|---------------------|-----------------------------|-------------------------|-----|
| Asn Ile Ile Leu Tyr | His Leu Thr Pro Gly         | Val Phe Ile Gly Lys Gly |     |
| 565                 | 570                         | 575                     |     |
| Phe Glu Pro Gly Val | Thr Asn Ile Leu Lys Thr     | Thr Gln Gly Ser Lys     |     |
| 580                 | 585                         | 590                     |     |
| Ile Phe Leu Lys Glu | Val Asn Asp Thr Leu Leu Val | Asn Glu Leu Lys         |     |
| 595                 | 600                         | 605                     |     |
| Ser Lys Glu Ser Asp | Ile Met Thr Thr Asn Gly     | Val Ile His Val Val     |     |
| 610                 | 615                         | 620                     |     |
| Asp Lys Leu Leu Tyr | Pro Ala Asp Thr Pro         | Val Gly Asn Asp Gln Leu |     |
| 625                 | 630                         | 635                     | 640 |
| Leu Glu Ile Leu Asn | Lys Leu Ile Lys Tyr         | Ile Gln Ile Lys Phe Val |     |
| 645                 | 650                         | 655                     |     |
| Arg Gly Ser Thr Phe | Lys Glu Ile Pro Val Thr     | Val Tyr Arg Pro Thr     |     |
| 660                 | 665                         | 670                     |     |
| Leu Thr Lys Val Lys | Ile Glu Gly Glu Pro Glu     | Phe Arg Leu Ile Lys     |     |
| 675                 | 680                         | 685                     |     |
| Glu Gly Glu Thr Ile | Thr Glu Val Ile His Gly     | Glu Pro Ile Ile Lys     |     |
| 690                 | 695                         | 700                     |     |
| Lys Tyr Thr Lys Ile | Ile Asp Gly Val Pro         | Val Glu Ile Thr Glu Lys |     |
| 705                 | 710                         | 715                     | 720 |
| Glu Thr Arg Glu Glu | Arg Ile Ile Thr Gly         | Pro Glu Ile Lys Tyr Thr |     |
| 725                 | 730                         | 735                     |     |
| Arg Ile Ser Thr Gly | Gly Gly Glu Thr Glu         | Glu Thr Leu Lys Lys Leu |     |
| 740                 | 745                         | 750                     |     |
| Leu Gln Glu Asp Thr | Pro Val Arg Lys Leu         | Gln Ala Asn Lys Lys Val |     |
| 755                 | 760                         | 765                     |     |
| Gln Gly Ser Arg Arg | Arg Leu Arg Glu Gly         | Arg Ser Gln             |     |
| 770                 | 775                         | 780                     |     |

<210> SEQ ID NO 43  
 <211> LENGTH: 3042  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (12) ... (2351)

<400> SEQUENCE: 43

|                                                                  |     |
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| agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg | 50  |
| Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu              |     |
| 1 5 10                                                           |     |
| ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg  | 98  |
| Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu  |     |
| 15 20 25                                                         |     |
| gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc  | 146 |
| Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala  |     |
| 30 35 40 45                                                      |     |
| ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag  | 194 |
| Leu Gln Gln Ile Leu Gly Thr Lys Lys Tyr Phe Ser Thr Cys Lys      |     |
| 50 55 60                                                         |     |
| aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat  | 242 |
| Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr  |     |
| 65 70 75                                                         |     |
| gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca  | 290 |

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| Glu | Cys | Cys | Pro | Gly | Tyr | Met | Arg | Met | Glu | Gly | Met | Lys | Gly | Cys | Pro |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|     | 80  |     |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |      |
| gca | gtt | ttg | ccc | att | gac | cat | gtt | tat | ggc | act | ctg | ggc | atc | gtg | gga | 338  |
| Ala | Val | Leu | Pro | Ile | Asp | His | Val | Tyr | Gly | Thr | Leu | Gly | Ile | Val | Gly |      |
|     | 95  |     |     |     |     |     | 100 |     |     |     | 105 |     |     |     |     |      |
| gcc | acc | aca | acg | cag | cgc | tat | tct | gac | gcc | tca | aaa | ctg | agg | gag | gag | 386  |
| Ala | Thr | Thr | Thr | Gln | Arg | Tyr | Ser | Asp | Ala | Ser | Lys | Leu | Arg | Glu | Glu |      |
|     | 110 |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |      |
| atc | gag | gga | aag | gga | tcc | ttc | act | tac | ttt | gca | ccg | agt | aat | gag | gct | 434  |
| Ile | Glu | Gly | Lys | Gly | Ser | Phe | Thr | Tyr | Phe | Ala | Pro | Ser | Asn | Glu | Ala |      |
|     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |     | 140 |      |
| tgg | gac | aac | ttg | gat | tct | gat | atc | cgt | aga | ggg | ttg | gag | agc | aac | gtg | 482  |
| Trp | Asp | Asn | Leu | Asp | Ser | Asp | Ile | Arg | Arg | Gly | Leu | Glu | Ser | Asn | Val |      |
|     |     |     | 145 |     |     |     |     | 150 |     |     |     |     |     | 155 |     |      |
| aat | gtt | gaa | tta | ctg | aat | gct | tta | cat | agt | cac | atg | att | aat | aag | aga | 530  |
| Asn | Val | Glu | Leu | Leu | Asn | Ala | Leu | His | Ser | His | Met | Ile | Asn | Lys | Arg |      |
|     |     | 160 |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |      |
| atg | ttg | acc | aag | gac | tta | aaa | aat | ggc | atg | att | att | cct | tca | atg | tat | 578  |
| Met | Leu | Thr | Lys | Asp | Leu | Lys | Asn | Gly | Met | Ile | Ile | Pro | Ser | Met | Tyr |      |
|     | 175 |     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |      |
| aac | aat | ttg | ggg | ctt | ttc | att | aac | cat | tat | cct | aat | ggg | gtt | gtc | act | 626  |
| Asn | Asn | Leu | Gly | Leu | Phe | Ile | Asn | His | Tyr | Pro | Asn | Gly | Val | Val | Thr |      |
|     | 190 |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |      |
| gtt | aat | tgt | gct | cga | atc | atc | cat | ggg | aac | cag | att | gca | aca | aat | ggg | 674  |
| Val | Asn | Cys | Ala | Arg | Ile | Ile | His | Gly | Asn | Gln | Ile | Ala | Thr | Asn | Gly |      |
|     |     |     | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |      |
| gtt | gtc | cat | gtc | att | gac | cgt | gtg | ctt | aca | caa | att | ggg | acc | tca | att | 722  |
| Val | Val | His | Val | Ile | Asp | Arg | Val | Leu | Thr | Gln | Ile | Gly | Thr | Ser | Ile |      |
|     |     |     | 225 |     |     |     |     | 230 |     |     |     |     |     | 235 |     |      |
| caa | gac | ttc | att | gaa | gca | gaa | gat | gac | ctt | tca | tct | ttt | aga | gca | gct | 770  |
| Gln | Asp | Phe | Ile | Glu | Ala | Glu | Asp | Asp | Leu | Ser | Ser | Phe | Arg | Ala | Ala |      |
|     |     | 240 |     |     |     |     | 245 |     |     |     |     |     | 250 |     |     |      |
| gcc | atc | aca | tcg | gac | ata | ttg | gag | gcc | ctt | gga | aga | gac | ggg | cac | ttc | 818  |
| Ala | Ile | Thr | Ser | Asp | Ile | Leu | Glu | Ala | Leu | Gly | Arg | Asp | Gly | His | Phe |      |
|     | 255 |     |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     |      |
| aca | ctc | ttt | gct | ccc | acc | aat | gag | gct | ttt | gag | aaa | ctt | cca | cga | ggg | 866  |
| Thr | Leu | Phe | Ala | Pro | Thr | Asn | Glu | Ala | Phe | Glu | Lys | Leu | Pro | Arg | Gly |      |
|     | 270 |     |     |     |     | 275 |     |     |     | 280 |     |     |     |     | 285 |      |
| gtc | cta | gaa | agg | atc | atg | gga | gac | aaa | gtg | gct | tcc | gaa | gct | ctt | atg | 914  |
| Val | Leu | Glu | Arg | Ile | Met | Gly | Asp | Lys | Val | Ala | Ser | Glu | Ala | Leu | Met |      |
|     |     |     | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |      |
| aag | tac | cac | atc | tta | aat | act | ctc | cag | tgt | tct | gag | tct | att | atg | gga | 962  |
| Lys | Tyr | His | Ile | Leu | Asn | Thr | Leu | Gln | Cys | Ser | Glu | Ser | Ile | Met | Gly |      |
|     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |      |
| gga | gca | gtc | ttt | gag | acg | ctg | gaa | gga | aat | aca | att | gag | ata | gga | tgt | 1010 |
| Gly | Ala | Val | Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys |      |
|     |     | 320 |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |      |
| gac | ggg | gac | agt | ata | aca | gta | aat | gga | atc | aaa | atg | gtg | aac | aaa | aag | 1058 |
| Asp | Gly | Asp | Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys |      |
|     | 335 |     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     |      |
| gat | att | gtg | aca | aat | aat | ggg | gtg | atc | cat | ttg | att | gat | cag | gtc | cta | 1106 |
| Asp | Ile | Val | Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu |      |
|     | 350 |     |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |      |
| att | cct | gat | tct | gcc | aaa | caa | gtt | att | gag | ctg | gct | gga | aaa | cag | caa | 1154 |
| Ile | Pro | Asp | Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln |      |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |      |
| acc | acc | ttc | acg | gat | ctt | gtg | gcc | caa | tta | ggc | ttg | gca | tct | gct | ctg | 1202 |

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| Thr | Thr | Phe | Thr | Asp | Leu  | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu |      |
|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|     |     |     | 385 |     |      |     |     | 390 |     |     |     |     | 395 |     |     |      |
| agg | cca | gat | gga | gaa | tac  | act | ttg | ctg | gca | cct | gtg | aat | aat | gca | ttt | 1250 |
| Arg | Pro | Asp | Gly | Glu | Tyr  | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe |      |
|     |     | 400 |     |     |      |     | 405 |     |     |     |     | 410 |     |     |     |      |
| tct | gat | gat | act | ctc | agc  | atg | gat | cag | cgc | ctc | ctt | aaa | tta | att | ctg | 1298 |
| Ser | Asp | Asp | Thr | Leu | Ser  | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu |      |
|     |     | 415 |     |     |      | 420 |     |     |     |     | 425 |     |     |     |     |      |
| cag | aat | cac | ata | ttg | aaa  | gta | aaa | gtt | ggc | ctt | aat | gag | ctt | tac | aac | 1346 |
| Gln | Asn | His | Ile | Leu | Lys  | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn |      |
| 430 |     |     |     |     | 435  |     |     |     |     | 440 |     |     |     |     | 445 |      |
| ggg | caa | ata | ctg | gaa | acc  | atc | gga | ggc | aaa | cag | ctc | aga | gtc | ttc | gta | 1394 |
| Gly | Gln | Ile | Leu | Glu | Thr  | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val |      |
|     |     |     |     | 450 |      |     |     |     | 455 |     |     |     |     | 460 |     |      |
| tat | cgt | aca | gct | gtc | tgc  | att | gaa | aat | tca | tgc | atg | gag | aaa | ggg | agt | 1442 |
| Tyr | Arg | Thr | Ala | Val | Cys  | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser |      |
|     |     |     | 465 |     |      |     |     | 470 |     |     |     |     | 475 |     |     |      |
| aag | caa | ggg | aga | aac | ggg  | gcg | att | cac | ata | ttc | cgc | gag | atc | atc | aag | 1490 |
| Lys | Gln | Gly | Arg | Asn | Gly  | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys |      |
|     |     | 480 |     |     |      |     | 485 |     |     |     |     | 490 |     |     |     |      |
| cca | gca | gag | aaa | tcc | ctc  | cat | gaa | aag | tta | aaa | caa | gat | aag | cgc | ttt | 1538 |
| Pro | Ala | Glu | Lys | Ser | Leu  | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe |      |
|     |     | 495 |     |     |      | 500 |     |     |     |     | 505 |     |     |     |     |      |
| agc | acc | ttc | ctc | agc | cta  | ctt | gaa | gct | gca | gac | ttg | aaa | gag | ctc | ctg | 1586 |
| Ser | Thr | Phe | Leu | Ser | Leu  | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu |      |
| 510 |     |     |     |     | 515  |     |     |     |     | 520 |     |     |     |     | 525 |      |
| aca | caa | cct | gga | gac | tggt | aca | tta | ttt | gtg | cca | acc | aat | gat | gct | ttt | 1634 |
| Thr | Gln | Pro | Gly | Asp | Trp  | Thr | Leu | Phe | Val | Pro | Thr | Asn | Asp | Ala | Phe |      |
|     |     |     |     | 530 |      |     |     |     | 535 |     |     |     |     | 540 |     |      |
| aag | gga | atg | act | agt | gaa  | gaa | aaa | gaa | att | ctg | ata | cgg | gac | aaa | aat | 1682 |
| Lys | Gly | Met | Thr | Ser | Glu  | Glu | Lys | Glu | Ile | Leu | Ile | Arg | Asp | Lys | Asn |      |
|     |     |     | 545 |     |      |     |     | 550 |     |     |     |     | 555 |     |     |      |
| gct | ctt | caa | aac | atc | att  | ctt | tat | cac | ctg | aca | cca | gga | gtt | ttc | att | 1730 |
| Ala | Leu | Gln | Asn | Ile | Ile  | Leu | Tyr | His | Leu | Thr | Pro | Gly | Val | Phe | Ile |      |
|     |     | 560 |     |     |      |     | 565 |     |     |     |     | 570 |     |     |     |      |
| gga | aaa | gga | ttt | gaa | cct  | ggg | gtt | act | aac | att | tta | aag | acc | aca | caa | 1778 |
| Gly | Lys | Gly | Phe | Glu | Pro  | Gly | Val | Thr | Asn | Ile | Leu | Lys | Thr | Thr | Gln |      |
|     |     | 575 |     |     |      | 580 |     |     |     |     | 585 |     |     |     |     |      |
| gga | agc | aaa | atc | ttt | ctg  | aaa | gaa | gta | aat | gat | aca | ctt | ctg | gtg | aat | 1826 |
| Gly | Ser | Lys | Ile | Phe | Leu  | Lys | Glu | Val | Asn | Asp | Thr | Leu | Leu | Val | Asn |      |
| 590 |     |     |     |     | 595  |     |     |     |     | 600 |     |     |     |     | 605 |      |
| gaa | ttg | aaa | tca | aaa | gaa  | tct | gac | atc | atg | aca | aca | aat | ggg | gta | att | 1874 |
| Glu | Leu | Lys | Ser | Lys | Glu  | Ser | Asp | Ile | Met | Thr | Thr | Asn | Gly | Val | Ile |      |
|     |     |     | 610 |     |      |     |     |     | 615 |     |     |     |     | 620 |     |      |
| cat | gtt | gta | gat | aaa | ctc  | ctc | tat | cca | gca | gac | aca | cct | gtt | gga | aat | 1922 |
| His | Val | Val | Asp | Lys | Leu  | Leu | Tyr | Pro | Ala | Asp | Thr | Pro | Val | Gly | Asn |      |
|     |     |     | 625 |     |      |     |     | 630 |     |     |     |     |     | 635 |     |      |
| gat | caa | ctg | ctg | gaa | ata  | ctt | aat | aaa | tta | atc | aaa | tac | atc | caa | att | 1970 |
| Asp | Gln | Leu | Leu | Glu | Ile  | Leu | Asn | Lys | Leu | Ile | Lys | Tyr | Ile | Gln | Ile |      |
|     |     | 640 |     |     |      |     | 645 |     |     |     |     | 650 |     |     |     |      |
| aag | ttt | gtt | cgt | ggg | agc  | acc | ttc | aaa | gaa | atc | ccc | gtg | act | gtc | tat | 2018 |
| Lys | Phe | Val | Arg | Gly | Ser  | Thr | Phe | Lys | Glu | Ile | Pro | Val | Thr | Val | Tyr |      |
|     |     | 655 |     |     |      | 660 |     |     |     |     | 665 |     |     |     |     |      |
| aag | cca | att | att | aaa | aaa  | tac | acc | aaa | atc | att | gat | gga | gtg | cct | gtg | 2066 |
| Lys | Pro | Ile | Ile | Lys | Lys  | Tyr | Thr | Lys | Ile | Ile | Asp | Gly | Val | Pro | Val |      |
|     |     | 670 |     |     | 675  |     |     |     |     | 680 |     |     |     | 685 |     |      |
| gaa | ata | act | gaa | aaa | gag  | aca | cga | gaa | gaa | cga | atc | att | aca | ggg | cct | 2114 |

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|             |            |             |             |             |            |             |
|-------------|------------|-------------|-------------|-------------|------------|-------------|
| Glu Ile Thr | Glu Lys    | Glu Thr Arg | Glu Glu Arg | Ile Ile Thr | Gly Pro    |             |
|             | 690        |             | 695         |             | 700        |             |
| gaa ata aaa | tac act    | agg att     | tct act     | gga ggt     | gga gaa    | aca gaa gaa |
| Glu Ile Lys | Tyr Thr    | Arg Ile     | Ser Thr     | Gly Gly     | Gly Glu    | Thr Glu Glu |
|             | 705        |             | 710         |             | 715        |             |
| act ctg aag | aaa ttg    | tta caa     | gaa gag     | gtc acc     | aag gtc    | acc aaa ttc |
| Thr Leu Lys | Lys Leu    | Leu Gln     | Glu Glu     | Val Thr     | Lys Val    | Thr Lys Phe |
|             | 720        |             | 725         |             | 730        |             |
| att gaa ggt | ggt gat    | ggt cat     | tta ttt     | gaa gat     | gaa gaa    | att aaa aga |
| Ile Glu Gly | Gly Asp    | Gly His     | Leu Phe     | Glu Asp     | Glu Glu    | Ile Lys Arg |
|             | 735        |             | 740         |             | 745        |             |
| ctg ctt cag | gga gac    | aca ccc     | gtg agg     | aag ttg     | caa gcc    | aac aaa aaa |
| Leu Leu Gln | Gly Asp    | Thr Pro     | Val Arg     | Lys Leu     | Gln Ala    | Asn Lys Lys |
|             | 750        |             | 755         |             | 760        | 765         |
| gtt caa ggt | tct aga    | aga cga     | tta agg     | gaa ggt     | cgt tct    | cag tga     |
| Val Gln Gly | Ser Arg    | Arg Arg     | Leu Arg     | Glu Gly     | Arg Ser    | Gln *       |
|             | 770        |             | 775         |             |            |             |
| aaatccaaaa  | accagaaaa  | aatgtttata  | caaccctaag  | tcaataacct  | gaccttagaa |             |
| aattgtgaga  | gccaagtgtg | cttcaggaac  | tgaacatca   | gcacaaagaa  | gcaatcatca |             |
| aataattctg  | aacacaaatt | taatattttt  | ttttctgaat  | gagaacatg   | agggaattg  |             |
| tggagttagc  | ctcctgtggt | aaaggaattg  | aagaaaatat  | aacaccttac  | accctttttc |             |
| atcttgacat  | taaaagtctt | ggctaacttt  | ggaatccatt  | agagaaaaat  | ccttgtcacc |             |
| agattcatta  | caattcaaat | cgaagagttg  | tgaactgtta  | tcccattgaa  | aagaccgagc |             |
| cttgatatga  | tgttatggat | acataaaatg  | cacgcaagcc  | attatctctc  | catgggaagc |             |
| taagttataa  | aaataggtgc | ttggtgtaca  | aaacttttta  | tatcaaaagg  | ctttgcacat |             |
| ttctatatga  | gtgggtttac | tggtaaatta  | tgttattttt  | tacaactaat  | ttgtactct  |             |
| cagaatgttt  | gtcatatgct | tcttgcaatg  | catatttttt  | aatctcaaac  | gtttcaataa |             |
| aaccattttt  | cagatataaa | gagaattact  | tcaaattgag  | taattcagaa  | aaactcaaga |             |
| tttaagttaa  | aaagtgggtt | ggacttggga  | a           |             |            |             |

<210> SEQ ID NO 44  
 <211> LENGTH: 779  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 44

|             |         |         |         |         |         |             |
|-------------|---------|---------|---------|---------|---------|-------------|
| Met Ile Pro | Phe Leu | Pro Met | Phe Ser | Leu Leu | Leu Leu | Ile Val     |
| 1           | 5       |         | 10      |         |         | 15          |
| Asn Pro Ile | Asn Ala | Asn Asn | His Tyr | Asp Lys | Ile Leu | Ala His Ser |
|             | 20      |         | 25      |         | 30      |             |
| Arg Ile Arg | Gly Arg | Asp Gln | Gly Pro | Asn Val | Cys Ala | Leu Gln Gln |
|             | 35      |         | 40      |         | 45      |             |
| Ile Leu Gly | Thr Lys | Lys Lys | Tyr Phe | Ser Thr | Cys Lys | Asn Trp Tyr |
|             | 50      |         | 55      |         | 60      |             |
| Lys Lys Ser | Ile Cys | Gly Gln | Lys Thr | Thr Val | Leu Tyr | Glu Cys Cys |
|             | 65      |         | 70      |         | 75      | 80          |
| Pro Gly Tyr | Met Arg | Met Glu | Gly Met | Lys Gly | Cys Pro | Ala Val Leu |
|             | 85      |         | 90      |         | 95      |             |
| Pro Ile Asp | His Val | Tyr Gly | Thr Leu | Gly Ile | Val Gly | Ala Thr Thr |
|             | 100     |         | 105     |         | 110     |             |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gln | Arg | Tyr | Ser | Asp | Ala | Ser | Lys | Leu | Arg | Glu | Glu | Ile | Glu | Gly |
|     | 115 |     |     |     |     |     | 120 |     |     |     | 125 |     |     |     |     |
| Lys | Gly | Ser | Phe | Thr | Tyr | Phe | Ala | Pro | Ser | Asn | Glu | Ala | Trp | Asp | Asn |
|     | 130 |     |     |     |     | 135 |     |     |     | 140 |     |     |     |     |     |
| Leu | Asp | Ser | Asp | Ile | Arg | Arg | Gly | Leu | Glu | Ser | Asn | Val | Asn | Val | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Leu | Leu | Asn | Ala | Leu | His | Ser | His | Met | Ile | Asn | Lys | Arg | Met | Leu | Thr |
|     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Lys | Asp | Leu | Lys | Asn | Gly | Met | Ile | Ile | Pro | Ser | Met | Tyr | Asn | Asn | Leu |
|     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |     |
| Gly | Leu | Phe | Ile | Asn | His | Tyr | Pro | Asn | Gly | Val | Val | Thr | Val | Asn | Cys |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Ala | Arg | Ile | Ile | His | Gly | Asn | Gln | Ile | Ala | Thr | Asn | Gly | Val | Val | His |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Val | Ile | Asp | Arg | Val | Leu | Thr | Gln | Ile | Gly | Thr | Ser | Ile | Gln | Asp | Phe |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Ile | Glu | Ala | Glu | Asp | Asp | Leu | Ser | Ser | Phe | Arg | Ala | Ala | Ala | Ile | Thr |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Ser | Asp | Ile | Leu | Glu | Ala | Leu | Gly | Arg | Asp | Gly | His | Phe | Thr | Leu | Phe |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ala | Pro | Thr | Asn | Glu | Ala | Phe | Glu | Lys | Leu | Pro | Arg | Gly | Val | Leu | Glu |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Arg | Ile | Met | Gly | Asp | Lys | Val | Ala | Ser | Glu | Ala | Leu | Met | Lys | Tyr | His |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ile | Leu | Asn | Thr | Leu | Gln | Cys | Ser | Glu | Ser | Ile | Met | Gly | Gly | Ala | Val |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys | Asp | Gly | Asp |
|     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys | Asp | Ile | Val |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu | Ile | Pro | Asp |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln | Thr | Thr | Phe |
|     | 370 |     |     |     |     |     | 375 |     |     |     | 380 |     |     |     |     |
| Thr | Asp | Leu | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu | Arg | Pro | Asp |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Gly | Glu | Tyr | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe | Ser | Asp | Asp |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Thr | Leu | Ser | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu | Gln | Asn | His |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ile | Leu | Lys | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn | Gly | Gln | Ile |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Leu | Glu | Thr | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val | Tyr | Arg | Thr |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Val | Cys | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser | Lys | Gln | Gly |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Arg | Asn | Gly | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys | Pro | Ala | Glu |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Lys | Ser | Leu | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe | Ser | Thr | Phe |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Leu | Ser | Leu | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu | Thr | Gln | Pro |

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| 515                                                             | 520 | 525 |     |
|-----------------------------------------------------------------|-----|-----|-----|
| Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met |     |     |     |
| 530                                                             | 535 | 540 |     |
| Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln |     |     |     |
| 545                                                             | 550 | 555 | 560 |
| Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu |     |     |     |
|                                                                 | 625 | 630 | 635 |
| Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Lys Pro Ile |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile Thr |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys |     |     |     |
|                                                                 | 705 | 710 | 715 |
| Lys Leu Leu Gln Glu Glu Val Thr Lys Val Thr Lys Phe Ile Glu Gly |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Gly Asp Gly His Leu Phe Glu Asp Glu Glu Ile Lys Arg Leu Leu Gln |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Gly Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln                     |     |     |     |
|                                                                 | 770 | 775 |     |

&lt;210&gt; SEQ ID NO 45

&lt;211&gt; LENGTH: 2958

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: human

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: CDS

&lt;222&gt; LOCATION: (12) ... (2267)

&lt;400&gt; SEQUENCE: 45

|                                                                  |     |
|------------------------------------------------------------------|-----|
| agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg | 50  |
| Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu                  |     |
| 1 5 10                                                           |     |
| ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg  | 98  |
| Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu  |     |
| 15 20 25                                                         |     |
| gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc  | 146 |
| Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala  |     |
| 30 35 40 45                                                      |     |
| ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag  | 194 |
| Leu Gln Gln Ile Leu Gly Thr Lys Lys Tyr Phe Ser Thr Cys Lys      |     |
| 50 55 60                                                         |     |

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|                                                                  |      |
|------------------------------------------------------------------|------|
| aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat  | 242  |
| Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr  |      |
| 65 70 75                                                         |      |
| gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca  | 290  |
| Glu Cys Cys Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro  |      |
| 80 85 90                                                         |      |
| gca gtt ttg ccc att gac cat gtt tat ggc act ctg ggc atc gtg gga  | 338  |
| Ala Val Leu Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly  |      |
| 95 100 105                                                       |      |
| gcc acc aca acg cag cgc tat tct gac gcc tca aaa ctg agg gag gag  | 386  |
| Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu  |      |
| 110 115 120 125                                                  |      |
| atc gag gga aag gga tcc ttc act tac ttt gca ccg agt aat gag gct  | 434  |
| Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala  |      |
| 130 135 140                                                      |      |
| tggt gac aac ttg gat tct gat atc cgt aga ggt ttg gag agc aac gtg | 482  |
| Trp Asp Asn Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val  |      |
| 145 150 155                                                      |      |
| aat gtt gaa tta ctg aat gct tta cat agt cac atg att aat aag aga  | 530  |
| Asn Val Glu Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg  |      |
| 160 165 170                                                      |      |
| atg ttg acc aag gac tta aaa aat ggc atg att att cct tca atg tat  | 578  |
| Met Leu Thr Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr  |      |
| 175 180 185                                                      |      |
| aac aat ttg ggg ctt ttc att aac cat tat cct aat ggg gtt gtc act  | 626  |
| Asn Asn Leu Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr  |      |
| 190 195 200 205                                                  |      |
| gtt aat tgt gct cga atc atc cat ggg aac cag att gca aca aat ggt  | 674  |
| Val Asn Cys Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly  |      |
| 210 215 220                                                      |      |
| gtt gtc cat gtc att gac cgt gtg ctt aca caa att ggt acc tca att  | 722  |
| Val Val His Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile  |      |
| 225 230 235                                                      |      |
| caa gac ttc att gaa gca gaa gat gac ctt tca tct ttt aga gca gct  | 770  |
| Gln Asp Phe Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala  |      |
| 240 245 250                                                      |      |
| gcc atc aca tcg gac ata ttg gag gcc ctt gga aga gac ggt cac ttc  | 818  |
| Ala Ile Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe  |      |
| 255 260 265                                                      |      |
| aca ctc ttt gct ccc acc aat gag gct ttt gag aaa ctt cca cga ggt  | 866  |
| Thr Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly  |      |
| 270 275 280 285                                                  |      |
| gtc cta gaa agg atc atg gga gac aaa gtg gct tcc gaa gct ctt atg  | 914  |
| Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met  |      |
| 290 295 300                                                      |      |
| aag tac cac atc tta aat act ctc cag tgt tct gag tct att atg gga  | 962  |
| Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly  |      |
| 305 310 315                                                      |      |
| gga gca gtc ttt gag acg ctg gaa gga aat aca att gag ata gga tgt  | 1010 |
| Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys  |      |
| 320 325 330                                                      |      |
| gac ggt gac agt ata aca gta aat gga atc aaa atg gtg aac aaa aag  | 1058 |
| Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys  |      |
| 335 340 345                                                      |      |
| gat att gtg aca aat aat ggt gtg atc cat ttg att gat cag gtc cta  | 1106 |
| Asp Ile Val Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu  |      |
| 350 355 360 365                                                  |      |

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| att cct gat tct gcc aaa caa gtt att gag ctg gct gga aaa cag caa<br>Ile Pro Asp Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln<br>370 375 380     | 1154 |
| acc acc ttc acg gat ctt gtg gcc caa tta ggc ttg gca tct gct ctg<br>Thr Thr Phe Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu<br>385 390 395     | 1202 |
| agg cca gat gga gaa tac act ttg ctg gca cct gtg aat aat gca ttt<br>Arg Pro Asp Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe<br>400 405 410     | 1250 |
| tct gat gat act ctc agc atg gat cag cgc ctc ctt aaa tta att ctg<br>Ser Asp Asp Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu<br>415 420 425     | 1298 |
| cag aat cac ata ttg aaa gta aaa gtt ggc ctt aat gag ctt tac aac<br>Gln Asn His Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn<br>430 435 440 445 | 1346 |
| ggg caa ata ctg gaa acc atc gga ggc aaa cag ctc aga gtc ttc gta<br>Gly Gln Ile Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val<br>450 455 460     | 1394 |
| tat cgt aca gct gtc tgc att gaa aat tca tgc atg gag aaa ggg agt<br>Tyr Arg Thr Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser<br>465 470 475     | 1442 |
| aag caa ggg aga aac ggt gcg att cac ata ttc cgc gag atc atc aag<br>Lys Gln Gly Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys<br>480 485 490     | 1490 |
| cca gca gag aaa tcc ctc cat gaa aag tta aaa caa gat aag cgc ttt<br>Pro Ala Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe<br>495 500 505     | 1538 |
| agc acc ttc ctc agc cta ctt gaa gct gca gac ttg aaa gag ctc ctg<br>Ser Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu<br>510 515 520 525 | 1586 |
| aca caa cct gga gac tgg aca tta ttt gtg cca acc aat gat gct ttt<br>Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe<br>530 535 540     | 1634 |
| aag gga atg act agt gaa gaa aaa gaa att ctg ata cgg gac aaa aat<br>Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn<br>545 550 555     | 1682 |
| gct ctt caa aac atc att ctt tat cac ctg aca cca gga gtt ttc att<br>Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile<br>560 565 570     | 1730 |
| gga aaa gga ttt gaa cct ggt gtt act aac att tta aag acc aca caa<br>Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln<br>575 580 585     | 1778 |
| gga agc aaa atc ttt ctg aaa gaa gta aat gat aca ctt ctg gtg aat<br>Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn<br>590 595 600 605 | 1826 |
| gaa ttg aaa tca aaa gaa tct gac atc atg aca aca aat ggt gta att<br>Glu Leu Lys Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile<br>610 615 620     | 1874 |
| cat gtt gta gat aaa ctc ctc tat cca gca gac aca cct gtt gga aat<br>His Val Val Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn<br>625 630 635     | 1922 |
| gat caa ctg ctg gaa ata ctt aat aaa tta atc aaa tac atc caa att<br>Asp Gln Leu Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile<br>640 645 650     | 1970 |
| aag ttt gtt cgt ggt agc acc ttc aaa gaa atc ccc gtg act gtc tat<br>Lys Phe Val Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr<br>655 660 665     | 2018 |

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aag cca att att aaa aaa tac acc aaa atc att gat gga gtg cct gtg      2066
Lys Pro Ile Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val
670                      675                      680                      685

gaa ata act gaa aaa gag aca cga gaa gaa cga atc att aca ggt cct      2114
Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro
                      690                      695                      700

gaa ata aaa tac act agg att tct act gga ggt gga gaa aca gaa gaa      2162
Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu
                      705                      710                      715

act ctg aag aaa ttg tta caa gaa gac aca ccc gtg agg aag ttg caa      2210
Thr Leu Lys Lys Leu Leu Gln Glu Asp Thr Pro Val Arg Lys Leu Gln
                      720                      725                      730

gcc aac aaa aaa gtt caa ggt tct aga aga cga tta agg gaa ggt cgt      2258
Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu Gly Arg
                      735                      740                      745

tct cag tga aaatccaaaa accagaaaaa aatgtttata caaccctaag      2307
Ser Gln *
750

tcaataacct gaccttagaa aattgtgaga gccaaagtga cttcaggaac tgaacatca      2367

gcacaaagaa gcaatcatca aataattctg aacacaaatt taatatTTTT ttttctgaat      2427

gagaaacatg agggaaattg tggagttagc ctctgtggtt aaaggaattg aagaaaatat      2487

aacaccttac accctttttc atcttgacat taaaagttct ggctaacttt ggaatccatt      2547

agagaaaaat cctgtgcacc agattcatta caattcaaat cgaagagttg tgaactgtta      2607

tcccatgtaa aagaccgagc cttgtatgta tggtatggat acataaaatg cagcaagcc      2667

attatctctc catgggaagc taagtataaa aaataggtgc ttggtgtaca aaacttttta      2727

tatcaaaagg ctttgcacat ttctatatga gtgggtttac tggtaaatta tgttattttt      2787

tacaactaat tttgtactct cagaatgttt gtcatatgct tcttgcaatg catatttttt      2847

aatctcaaac gtttcaataa aaccattttt cagatataaa gagaattact tcaaattgag      2907

taattcagaa aaactcaaga ttttaagttaa aaagtggttt ggacttggga a      2958

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<210> SEQ ID NO 46
<211> LENGTH: 751
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 46

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Ile Val
1                      5                      10                      15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20                      25                      30

Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35                      40                      45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50                      55                      60

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65                      70                      75                      80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85                      90                      95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100                      105                      110

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gln | Arg | Tyr | Ser | Asp | Ala | Ser | Lys | Leu | Arg | Glu | Glu | Ile | Glu | Gly |
|     | 115 |     |     |     |     |     | 120 |     |     |     | 125 |     |     |     |     |
| Lys | Gly | Ser | Phe | Thr | Tyr | Phe | Ala | Pro | Ser | Asn | Glu | Ala | Trp | Asp | Asn |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Leu | Asp | Ser | Asp | Ile | Arg | Arg | Gly | Leu | Glu | Ser | Asn | Val | Asn | Val | Glu |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Leu | Leu | Asn | Ala | Leu | His | Ser | His | Met | Ile | Asn | Lys | Arg | Met | Leu | Thr |
|     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Lys | Asp | Leu | Lys | Asn | Gly | Met | Ile | Ile | Pro | Ser | Met | Tyr | Asn | Asn | Leu |
|     |     | 180 |     |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Gly | Leu | Phe | Ile | Asn | His | Tyr | Pro | Asn | Gly | Val | Val | Thr | Val | Asn | Cys |
|     | 195 |     |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Ala | Arg | Ile | Ile | His | Gly | Asn | Gln | Ile | Ala | Thr | Asn | Gly | Val | Val | His |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Val | Ile | Asp | Arg | Val | Leu | Thr | Gln | Ile | Gly | Thr | Ser | Ile | Gln | Asp | Phe |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Ile | Glu | Ala | Glu | Asp | Asp | Leu | Ser | Ser | Phe | Arg | Ala | Ala | Ala | Ile | Thr |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Ser | Asp | Ile | Leu | Glu | Ala | Leu | Gly | Arg | Asp | Gly | His | Phe | Thr | Leu | Phe |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ala | Pro | Thr | Asn | Glu | Ala | Phe | Glu | Lys | Leu | Pro | Arg | Gly | Val | Leu | Glu |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Arg | Ile | Met | Gly | Asp | Lys | Val | Ala | Ser | Glu | Ala | Leu | Met | Lys | Tyr | His |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ile | Leu | Asn | Thr | Leu | Gln | Cys | Ser | Glu | Ser | Ile | Met | Gly | Gly | Ala | Val |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys | Asp | Gly | Asp |
|     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys | Asp | Ile | Val |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu | Ile | Pro | Asp |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln | Thr | Thr | Phe |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Thr | Asp | Leu | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu | Arg | Pro | Asp |
| 385 |     |     |     |     | 390 |     |     |     | 395 |     |     |     |     | 400 |     |
| Gly | Glu | Tyr | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe | Ser | Asp | Asp |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Thr | Leu | Ser | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu | Gln | Asn | His |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ile | Leu | Lys | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn | Gly | Gln | Ile |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Leu | Glu | Thr | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val | Tyr | Arg | Thr |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Val | Cys | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser | Lys | Gln | Gly |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     | 480 |     |
| Arg | Asn | Gly | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys | Pro | Ala | Glu |
|     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |     | 495 |     |
| Lys | Ser | Leu | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe | Ser | Thr | Phe |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Leu | Ser | Leu | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu | Thr | Gln | Pro |

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| 515                                                                                | 520 | 525 |
|------------------------------------------------------------------------------------|-----|-----|
| Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met<br>530 535 540     |     |     |
| Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln<br>545 550 555 560 |     |     |
| Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly<br>565 570 575     |     |     |
| Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys<br>580 585 590     |     |     |
| Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys<br>595 600 605     |     |     |
| Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val<br>610 615 620     |     |     |
| Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu<br>625 630 635 640 |     |     |
| Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val<br>645 650 655     |     |     |
| Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Lys Pro Ile<br>660 665 670     |     |     |
| Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile Thr<br>675 680 685     |     |     |
| Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys<br>690 695 700     |     |     |
| Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys<br>705 710 715 720 |     |     |
| Lys Leu Leu Gln Glu Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys<br>725 730 735     |     |     |
| Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln<br>740 745 750         |     |     |

&lt;210&gt; SEQ ID NO 47

&lt;211&gt; LENGTH: 2952

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: human

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: CDS

&lt;222&gt; LOCATION: (12) ... (2261)

&lt;400&gt; SEQUENCE: 47

|                                                                                                                                                   |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| agagactcaa g atg att ccc ttt tta ccc atg ttt tct cta cta ttg ctg<br>Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu<br>1 5 10                 | 50  |
| ctt att gtt aac cct ata aac gcc aac aat cat tat gac aag atc ttg<br>Leu Ile Val Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu<br>15 20 25    | 98  |
| gct cat agt cgt atc agg ggt cgg gac caa ggc cca aat gtc tgt gcc<br>Ala His Ser Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala<br>30 35 40 45 | 146 |
| ctt caa cag att ttg ggc acc aaa aag aaa tac ttc agc act tgt aag<br>Leu Gln Gln Ile Leu Gly Thr Lys Lys Tyr Phe Ser Thr Cys Lys<br>50 55 60        | 194 |
| aac tgg tat aaa aag tcc atc tgt gga cag aaa acg act gtg tta tat<br>Asn Trp Tyr Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr<br>65 70 75    | 242 |
| gaa tgt tgc cct ggt tat atg aga atg gaa gga atg aaa ggc tgc cca                                                                                   | 290 |

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| Glu | Cys | Cys | Pro | Gly | Tyr | Met | Arg | Met | Glu | Gly | Met | Lys | Gly | Cys | Pro |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|     | 80  |     |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |      |
| gca | gtt | ttg | ccc | att | gac | cat | gtt | tat | ggc | act | ctg | ggc | atc | gtg | gga | 338  |
| Ala | Val | Leu | Pro | Ile | Asp | His | Val | Tyr | Gly | Thr | Leu | Gly | Ile | Val | Gly |      |
|     | 95  |     |     |     |     |     | 100 |     |     |     | 105 |     |     |     |     |      |
| gcc | acc | aca | acg | cag | cgc | tat | tct | gac | gcc | tca | aaa | ctg | agg | gag | gag | 386  |
| Ala | Thr | Thr | Thr | Gln | Arg | Tyr | Ser | Asp | Ala | Ser | Lys | Leu | Arg | Glu | Glu |      |
|     | 110 |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |      |
| atc | gag | gga | aag | gga | tcc | ttc | act | tac | ttt | gca | ccg | agt | aat | gag | gct | 434  |
| Ile | Glu | Gly | Lys | Gly | Ser | Phe | Thr | Tyr | Phe | Ala | Pro | Ser | Asn | Glu | Ala |      |
|     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |      |
| tgg | gac | aac | ttg | gat | tct | gat | atc | cgt | aga | ggg | ttg | gag | agc | aac | gtg | 482  |
| Trp | Asp | Asn | Leu | Asp | Ser | Asp | Ile | Arg | Arg | Gly | Leu | Glu | Ser | Asn | Val |      |
|     |     |     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |      |
| aat | gtt | gaa | tta | ctg | aat | gct | tta | cat | agt | cac | atg | att | aat | aag | aga | 530  |
| Asn | Val | Glu | Leu | Leu | Asn | Ala | Leu | His | Ser | His | Met | Ile | Asn | Lys | Arg |      |
|     |     | 160 |     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |      |
| atg | ttg | acc | aag | gac | tta | aaa | aat | ggc | atg | att | att | cct | tca | atg | tat | 578  |
| Met | Leu | Thr | Lys | Asp | Leu | Lys | Asn | Gly | Met | Ile | Ile | Pro | Ser | Met | Tyr |      |
|     | 175 |     |     |     |     | 180 |     |     |     | 185 |     |     |     |     |     |      |
| aac | aat | ttg | ggg | ctt | ttc | att | aac | cat | tat | cct | aat | ggg | gtt | gtc | act | 626  |
| Asn | Asn | Leu | Gly | Leu | Phe | Ile | Asn | His | Tyr | Pro | Asn | Gly | Val | Val | Thr |      |
|     | 190 |     |     |     | 195 |     |     |     | 200 |     |     |     |     | 205 |     |      |
| gtt | aat | tgt | gct | cga | atc | atc | cat | ggg | aac | cag | att | gca | aca | aat | ggg | 674  |
| Val | Asn | Cys | Ala | Arg | Ile | Ile | His | Gly | Asn | Gln | Ile | Ala | Thr | Asn | Gly |      |
|     |     |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |      |
| gtt | gtc | cat | gtc | att | gac | cgt | gtg | ctt | aca | caa | att | ggg | acc | tca | att | 722  |
| Val | Val | His | Val | Ile | Asp | Arg | Val | Leu | Thr | Gln | Ile | Gly | Thr | Ser | Ile |      |
|     |     |     | 225 |     |     |     | 230 |     |     |     |     |     | 235 |     |     |      |
| caa | gac | ttc | att | gaa | gca | gaa | gat | gac | ctt | tca | tct | ttt | aga | gca | gct | 770  |
| Gln | Asp | Phe | Ile | Glu | Ala | Glu | Asp | Asp | Leu | Ser | Ser | Phe | Arg | Ala | Ala |      |
|     | 240 |     |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |      |
| gcc | atc | aca | tcg | gac | ata | ttg | gag | gcc | ctt | gga | aga | gac | ggg | cac | ttc | 818  |
| Ala | Ile | Thr | Ser | Asp | Ile | Leu | Glu | Ala | Leu | Gly | Arg | Asp | Gly | His | Phe |      |
|     | 255 |     |     |     |     | 260 |     |     |     | 265 |     |     |     |     |     |      |
| aca | ctc | ttt | gct | ccc | acc | aat | gag | gct | ttt | gag | aaa | ctt | cca | cga | ggg | 866  |
| Thr | Leu | Phe | Ala | Pro | Thr | Asn | Glu | Ala | Phe | Glu | Lys | Leu | Pro | Arg | Gly |      |
|     | 270 |     |     |     | 275 |     |     |     | 280 |     |     |     |     | 285 |     |      |
| gtc | cta | gaa | agg | atc | atg | gga | gac | aaa | gtg | gct | tcc | gaa | gct | ctt | atg | 914  |
| Val | Leu | Glu | Arg | Ile | Met | Gly | Asp | Lys | Val | Ala | Ser | Glu | Ala | Leu | Met |      |
|     |     |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |      |
| aag | tac | cac | atc | tta | aat | act | ctc | cag | tgt | tct | gag | tct | att | atg | gga | 962  |
| Lys | Tyr | His | Ile | Leu | Asn | Thr | Leu | Gln | Cys | Ser | Glu | Ser | Ile | Met | Gly |      |
|     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |      |
| gga | gca | gtc | ttt | gag | acg | ctg | gaa | gga | aat | aca | att | gag | ata | gga | tgt | 1010 |
| Gly | Ala | Val | Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys |      |
|     |     | 320 |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |      |
| gac | ggg | gac | agt | ata | aca | gta | aat | gga | atc | aaa | atg | gtg | aac | aaa | aag | 1058 |
| Asp | Gly | Asp | Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys |      |
|     | 335 |     |     |     |     | 340 |     |     |     | 345 |     |     |     |     |     |      |
| gat | att | gtg | aca | aat | aat | ggg | gtg | atc | cat | ttg | att | gat | cag | gtc | cta | 1106 |
| Asp | Ile | Val | Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu |      |
|     | 350 |     |     |     | 355 |     |     |     |     | 360 |     |     |     | 365 |     |      |
| att | cct | gat | tct | gcc | aaa | caa | gtt | att | gag | ctg | gct | gga | aaa | cag | caa | 1154 |
| Ile | Pro | Asp | Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln |      |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |      |
| acc | acc | ttc | acg | gat | ctt | gtg | gcc | caa | tta | ggc | ttg | gca | tct | gct | ctg | 1202 |

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| Thr | Thr | Phe | Thr | Asp | Leu  | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu |      |
|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|     |     |     | 385 |     |      |     |     | 390 |     |     |     |     | 395 |     |     |      |
| agg | cca | gat | gga | gaa | tac  | act | ttg | ctg | gca | cct | gtg | aat | aat | gca | ttt | 1250 |
| Arg | Pro | Asp | Gly | Glu | Tyr  | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe |      |
|     |     | 400 |     |     |      |     | 405 |     |     |     |     | 410 |     |     |     |      |
| tct | gat | gat | act | ctc | agc  | atg | gat | cag | cgc | ctc | ctt | aaa | tta | att | ctg | 1298 |
| Ser | Asp | Asp | Thr | Leu | Ser  | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu |      |
|     |     | 415 |     |     |      | 420 |     |     |     |     | 425 |     |     |     |     |      |
| cag | aat | cac | ata | ttg | aaa  | gta | aaa | gtt | ggc | ctt | aat | gag | ctt | tac | aac | 1346 |
| Gln | Asn | His | Ile | Leu | Lys  | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn |      |
| 430 |     |     |     |     | 435  |     |     |     |     | 440 |     |     |     |     | 445 |      |
| ggg | caa | ata | ctg | gaa | acc  | atc | gga | ggc | aaa | cag | ctc | aga | gtc | ttc | gta | 1394 |
| Gly | Gln | Ile | Leu | Glu | Thr  | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val |      |
|     |     |     |     | 450 |      |     |     |     | 455 |     |     |     |     | 460 |     |      |
| tat | cgt | aca | gct | gtc | tgc  | att | gaa | aat | tca | tgc | atg | gag | aaa | ggg | agt | 1442 |
| Tyr | Arg | Thr | Ala | Val | Cys  | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser |      |
|     |     |     | 465 |     |      |     |     | 470 |     |     |     |     | 475 |     |     |      |
| aag | caa | ggg | aga | aac | ggg  | gcg | att | cac | ata | ttc | cgc | gag | atc | atc | aag | 1490 |
| Lys | Gln | Gly | Arg | Asn | Gly  | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys |      |
|     |     | 480 |     |     |      |     | 485 |     |     |     |     | 490 |     |     |     |      |
| cca | gca | gag | aaa | tcc | ctc  | cat | gaa | aag | tta | aaa | caa | gat | aag | cgc | ttt | 1538 |
| Pro | Ala | Glu | Lys | Ser | Leu  | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe |      |
|     |     | 495 |     |     |      | 500 |     |     |     |     | 505 |     |     |     |     |      |
| agc | acc | ttc | ctc | agc | cta  | ctt | gaa | gct | gca | gac | ttg | aaa | gag | ctc | ctg | 1586 |
| Ser | Thr | Phe | Leu | Ser | Leu  | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu |      |
| 510 |     |     |     |     | 515  |     |     |     |     | 520 |     |     |     |     | 525 |      |
| aca | caa | cct | gga | gac | tggt | aca | tta | ttt | gtg | cca | acc | aat | gat | gct | ttt | 1634 |
| Thr | Gln | Pro | Gly | Asp | Trp  | Thr | Leu | Phe | Val | Pro | Thr | Asn | Asp | Ala | Phe |      |
|     |     |     |     | 530 |      |     |     |     | 535 |     |     |     |     | 540 |     |      |
| aag | gga | atg | act | agt | gaa  | gaa | aaa | gaa | att | ctg | ata | cgg | gac | aaa | aat | 1682 |
| Lys | Gly | Met | Thr | Ser | Glu  | Glu | Lys | Glu | Ile | Leu | Ile | Arg | Asp | Lys | Asn |      |
|     |     |     | 545 |     |      |     |     | 550 |     |     |     |     | 555 |     |     |      |
| gct | ctt | caa | aac | atc | att  | ctt | tat | cac | ctg | aca | cca | gga | gtt | ttc | att | 1730 |
| Ala | Leu | Gln | Asn | Ile | Ile  | Leu | Tyr | His | Leu | Thr | Pro | Gly | Val | Phe | Ile |      |
|     |     | 560 |     |     |      |     | 565 |     |     |     |     | 570 |     |     |     |      |
| gga | aaa | gga | ttt | gaa | cct  | ggg | gtt | act | aac | att | tta | aag | acc | aca | caa | 1778 |
| Gly | Lys | Gly | Phe | Glu | Pro  | Gly | Val | Thr | Asn | Ile | Leu | Lys | Thr | Thr | Gln |      |
|     |     | 575 |     |     |      | 580 |     |     |     |     | 585 |     |     |     |     |      |
| gga | agc | aaa | atc | ttt | ctg  | aaa | gaa | gta | aat | gat | aca | ctt | ctg | gtg | aat | 1826 |
| Gly | Ser | Lys | Ile | Phe | Leu  | Lys | Glu | Val | Asn | Asp | Thr | Leu | Leu | Val | Asn |      |
| 590 |     |     |     |     | 595  |     |     |     | 600 |     |     |     |     |     | 605 |      |
| gaa | ttg | aaa | tca | aaa | gaa  | tct | gac | atc | atg | aca | aca | aat | ggg | gta | att | 1874 |
| Glu | Leu | Lys | Ser | Lys | Glu  | Ser | Asp | Ile | Met | Thr | Thr | Asn | Gly | Val | Ile |      |
|     |     |     | 610 |     |      |     |     |     | 615 |     |     |     |     | 620 |     |      |
| cat | gtt | gta | gat | aaa | ctc  | ctc | tat | cca | gca | gac | aca | cct | gtt | gga | aat | 1922 |
| His | Val | Val | Asp | Lys | Leu  | Leu | Tyr | Pro | Ala | Asp | Thr | Pro | Val | Gly | Asn |      |
|     |     |     | 625 |     |      |     |     | 630 |     |     |     |     |     | 635 |     |      |
| gat | caa | ctg | ctg | gaa | ata  | ctt | aat | aaa | tta | atc | aaa | tac | atc | caa | att | 1970 |
| Asp | Gln | Leu | Leu | Glu | Ile  | Leu | Asn | Lys | Leu | Ile | Lys | Tyr | Ile | Gln | Ile |      |
|     |     | 640 |     |     |      |     | 645 |     |     |     |     | 650 |     |     |     |      |
| aag | ttt | gtt | cgt | ggg | agc  | acc | ttc | aaa | gaa | atc | ccc | gtg | act | gtc | tat | 2018 |
| Lys | Phe | Val | Arg | Gly | Ser  | Thr | Phe | Lys | Glu | Ile | Pro | Val | Thr | Val | Tyr |      |
|     |     | 655 |     |     |      | 660 |     |     |     |     | 665 |     |     |     |     |      |
| agt | cct | gaa | ata | aaa | tac  | act | agg | att | tct | act | gga | ggg | gga | gaa | aca | 2066 |
| Ser | Pro | Glu | Ile | Lys | Tyr  | Thr | Arg | Ile | Ser | Thr | Gly | Gly | Gly | Glu | Thr |      |
| 670 |     |     |     |     | 675  |     |     |     |     | 680 |     |     |     |     | 685 |      |
| gaa | gaa | act | ctg | aag | aaa  | ttg | tta | caa | gaa | gag | gtc | acc | aag | gtc | acc | 2114 |

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| Glu   | Glu        | Thr        | Leu        | Lys        | Lys        | Leu        | Leu | Gln | Glu | Glu | Val | Thr | Lys | Val | Thr |      |
|-------|------------|------------|------------|------------|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|       |            |            | 690        |            |            |            |     | 695 |     |     |     |     |     | 700 |     |      |
| aaa   | ttc        | att        | gaa        | ggg        | ggg        | gat        | ggg | cat | tta | ttt | gaa | gat | gaa | gaa | att | 2162 |
| Lys   | Phe        | Ile        | Glu        | Gly        | Gly        | Asp        | Gly | His | Leu | Phe | Glu | Asp | Glu | Glu | Ile |      |
|       |            |            | 705        |            |            |            |     | 710 |     |     |     |     |     | 715 |     |      |
| aaa   | aga        | ctg        | ctt        | cag        | gga        | gac        | aca | ccc | gtg | agg | aag | ttg | caa | gcc | aac | 2210 |
| Lys   | Arg        | Leu        | Leu        | Gln        | Gly        | Asp        | Thr | Pro | Val | Arg | Lys | Leu | Gln | Ala | Asn |      |
|       |            |            | 720        |            |            |            |     | 725 |     |     |     |     |     | 730 |     |      |
| aaa   | aaa        | gtt        | caa        | ggg        | tct        | aga        | aga | cga | tta | agg | gaa | ggg | cgt | tct | cag | 2258 |
| Lys   | Lys        | Val        | Gln        | Gly        | Ser        | Arg        | Arg | Arg | Leu | Arg | Glu | Gly | Arg | Ser | Gln |      |
|       |            |            | 735        |            |            |            |     | 740 |     |     |     |     |     | 745 |     |      |
| tga   | aaatccaaaa | accagaaaaa | aatgtttata | caaccctaag | tcaataacct |            |     |     |     |     |     |     |     |     |     | 2311 |
| *     |            |            |            |            |            |            |     |     |     |     |     |     |     |     |     |      |
| gac   | cttagaa    | aattgtgaga | gccaaagtga | cttcaggaac | tgaacatca  | gcacaaagaa |     |     |     |     |     |     |     |     |     | 2371 |
| gca   | atcatca    | aataattctg | aacacaaatt | taatattttt | ttttctgaat | gagaaacatg |     |     |     |     |     |     |     |     |     | 2431 |
| agg   | gaaattg    | tggagtagc  | ctcctgtggt | aaaggaattg | aagaaaatat | aacaccttac |     |     |     |     |     |     |     |     |     | 2491 |
| acc   | cttttttc   | atcttgacat | taaaagttct | ggctaacttt | ggaatccatt | agagaaaaat |     |     |     |     |     |     |     |     |     | 2551 |
| cct   | gtcacc     | agattcatta | caattcaaat | cgaagagttg | tgaactgtta | tccattgaa  |     |     |     |     |     |     |     |     |     | 2611 |
| aag   | accgagc    | cttgtatgta | tggtatggat | acataaaatg | cacgcaagcc | attatctctc |     |     |     |     |     |     |     |     |     | 2671 |
| cat   | gggaagc    | taagttataa | aaataggtgc | ttggtgtaca | aaacttttta | tatcaaaagg |     |     |     |     |     |     |     |     |     | 2731 |
| ctt   | gcacat     | ttctatatga | gtgggtttac | tggtaaatta | tggtattttt | tacaactaat |     |     |     |     |     |     |     |     |     | 2791 |
| ttt   | gtactct    | cagaatgttt | gtcatatgct | tcttgcaatg | catatttttt | aatctcaaac |     |     |     |     |     |     |     |     |     | 2851 |
| gtt   | taataa     | aaccattttt | cagatataaa | gagaattact | tcaaattgag | taattcagaa |     |     |     |     |     |     |     |     |     | 2911 |
| aaact | caaga      | tttaagttaa | aaagtgggtt | ggacttgga  | a          |            |     |     |     |     |     |     |     |     |     | 2952 |

&lt;210&gt; SEQ ID NO 48

&lt;211&gt; LENGTH: 749

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 48

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | Pro | Phe | Leu | Pro | Met | Phe | Ser | Leu | Leu | Leu | Leu | Ile | Val |     |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     | 15  |     |     |
| Asn | Pro | Ile | Asn | Ala | Asn | Asn | His | Tyr | Asp | Lys | Ile | Leu | Ala | His | Ser |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Arg | Ile | Arg | Gly | Arg | Asp | Gln | Gly | Pro | Asn | Val | Cys | Ala | Leu | Gln | Gln |
|     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Ile | Leu | Gly | Thr | Lys | Lys | Lys | Tyr | Phe | Ser | Thr | Cys | Lys | Asn | Trp | Tyr |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Lys | Lys | Ser | Ile | Cys | Gly | Gln | Lys | Thr | Thr | Val | Leu | Tyr | Glu | Cys | Cys |
|     | 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Pro | Gly | Tyr | Met | Arg | Met | Glu | Gly | Met | Lys | Gly | Cys | Pro | Ala | Val | Leu |
|     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |     | 95  |     |
| Pro | Ile | Asp | His | Val | Tyr | Gly | Thr | Leu | Gly | Ile | Val | Gly | Ala | Thr | Thr |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Thr | Gln | Arg | Tyr | Ser | Asp | Ala | Ser | Lys | Leu | Arg | Glu | Glu | Ile | Glu | Gly |
|     |     |     | 115 |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Lys | Gly | Ser | Phe | Thr | Tyr | Phe | Ala | Pro | Ser | Asn | Glu | Ala | Trp | Asp | Asn |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Leu | Asp | Ser | Asp | Ile | Arg | Arg | Gly | Leu | Glu | Ser | Asn | Val | Asn | Val | Glu |

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| 145                                                             | 150                                             | 155 | 160 |
|-----------------------------------------------------------------|-------------------------------------------------|-----|-----|
| Leu Leu Asn Ala                                                 | Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr |     |     |
|                                                                 | 165                                             | 170 | 175 |
| Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu |                                                 |     |     |
|                                                                 | 180                                             | 185 | 190 |
| Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys |                                                 |     |     |
|                                                                 | 195                                             | 200 | 205 |
| Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His |                                                 |     |     |
|                                                                 | 210                                             | 215 | 220 |
| Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe |                                                 |     |     |
|                                                                 | 225                                             | 230 | 235 |
| Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr |                                                 |     |     |
|                                                                 | 245                                             | 250 | 255 |
| Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe |                                                 |     |     |
|                                                                 | 260                                             | 265 | 270 |
| Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu |                                                 |     |     |
|                                                                 | 275                                             | 280 | 285 |
| Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His |                                                 |     |     |
|                                                                 | 290                                             | 295 | 300 |
| Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val |                                                 |     |     |
|                                                                 | 305                                             | 310 | 315 |
| Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp |                                                 |     |     |
|                                                                 | 325                                             | 330 | 335 |
| Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val |                                                 |     |     |
|                                                                 | 340                                             | 345 | 350 |
| Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp |                                                 |     |     |
|                                                                 | 355                                             | 360 | 365 |
| Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe |                                                 |     |     |
|                                                                 | 370                                             | 375 | 380 |
| Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp |                                                 |     |     |
|                                                                 | 385                                             | 390 | 395 |
| Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp |                                                 |     |     |
|                                                                 | 405                                             | 410 | 415 |
| Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His |                                                 |     |     |
|                                                                 | 420                                             | 425 | 430 |
| Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile |                                                 |     |     |
|                                                                 | 435                                             | 440 | 445 |
| Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr |                                                 |     |     |
|                                                                 | 450                                             | 455 | 460 |
| Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly |                                                 |     |     |
|                                                                 | 465                                             | 470 | 475 |
| Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu |                                                 |     |     |
|                                                                 | 485                                             | 490 | 495 |
| Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe |                                                 |     |     |
|                                                                 | 500                                             | 505 | 510 |
| Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro |                                                 |     |     |
|                                                                 | 515                                             | 520 | 525 |
| Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met |                                                 |     |     |
|                                                                 | 530                                             | 535 | 540 |
| Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln |                                                 |     |     |
|                                                                 | 545                                             | 550 | 555 |
|                                                                 |                                                 |     | 560 |

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<210> SEQ ID NO 49
<211> LENGTH: 2868
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (12)...(2177)
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<400> SEQUENCE: 49

|            |      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| agagactcaa | g    | atg | att | ccc | ttt | tta | ccc | atg | ttt | tct | cta | cta | ttg | ctg | 50  |     |
|            |      | Met | Ile | Pro | Phe | Leu | Pro | Met | Phe | Ser | Leu | Leu | Leu | Leu |     |     |
|            |      | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     |
| ctt        | att  | gtt | aac | cct | ata | aac | gcc | aac | aat | cat | tat | gac | aag | atc | ttg | 98  |
| Leu        | Ile  | Val | Asn | Pro | Ile | Asn | Ala | Asn | Asn | His | Tyr | Asp | Lys | Ile | Leu |     |
|            |      | 15  |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     |
| gct        | cat  | agt | cgt | atc | agg | ggc | cgg | gac | caa | ggc | cca | aat | gtc | tgt | gcc | 146 |
| Ala        | His  | Ser | Arg | Ile | Arg | Gly | Arg | Asp | Gln | Gly | Pro | Asn | Val | Cys | Ala |     |
|            |      | 30  |     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |
| ctt        | caa  | cag | att | ttg | ggc | acc | aaa | aag | aaa | tac | ttc | agc | act | tgt | aag | 194 |
| Leu        | Gln  | Gln | Ile | Leu | Gly | Thr | Lys | Lys | Lys | Tyr | Phe | Ser | Thr | Cys | Lys |     |
|            |      |     |     | 50  |     |     |     |     |     | 55  |     |     |     | 60  |     |     |
| aac        | tggt | tat | aaa | aag | tcc | atc | tgt | gga | cag | aaa | acg | act | gtg | tta | tat | 242 |
| Asn        | Trp  | Tyr | Lys | Lys | Ser | Ile | Cys | Gly | Gln | Lys | Thr | Thr | Val | Leu | Tyr |     |
|            |      |     | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |
| gaa        | tgt  | tgc | cct | ggc | tat | atg | aga | atg | gaa | gga | atg | aaa | ggc | tgc | cca | 290 |
| Glu        | Cys  | Cys | Pro | Gly | Tyr | Met | Arg | Met | Glu | Gly | Met | Lys | Gly | Cys | Pro |     |
|            |      |     | 80  |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |
| gca        | gtt  | ttg | ccc | att | gac | cat | gtt | tat | ggc | act | ctg | ggc | atc | gtg | gga | 338 |
| Ala        | Val  | Leu | Pro | Ile | Asp | His | Val | Tyr | Gly | Thr | Leu | Gly | Ile | Val | Gly |     |
|            | 95   |     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     |

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|                                                                  |      |
|------------------------------------------------------------------|------|
| gcc acc aca acg cag cgc tat tct gac gcc tca aaa ctg agg gag gag  | 386  |
| Ala Thr Thr Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu  |      |
| 110 115 120 125                                                  |      |
| atc gag gga aag gga tcc ttc act tac ttt gca ccg agt aat gag gct  | 434  |
| Ile Glu Gly Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala  |      |
| 130 135 140                                                      |      |
| tggt gac aac ttg gat tct gat atc cgt aga ggt ttg gag agc aac gtg | 482  |
| Trp Asp Asn Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val  |      |
| 145 150 155                                                      |      |
| aat gtt gaa tta ctg aat gct tta cat agt cac atg att aat aag aga  | 530  |
| Asn Val Glu Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg  |      |
| 160 165 170                                                      |      |
| atg ttg acc aag gac tta aaa aat ggc atg att att cct tca atg tat  | 578  |
| Met Leu Thr Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr  |      |
| 175 180 185                                                      |      |
| aac aat ttg ggg ctt ttc att aac cat tat cct aat ggg gtt gtc act  | 626  |
| Asn Asn Leu Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr  |      |
| 190 195 200 205                                                  |      |
| gtt aat tgt gct cga atc atc cat ggg aac cag att gca aca aat ggt  | 674  |
| Val Asn Cys Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly  |      |
| 210 215 220                                                      |      |
| gtt gtc cat gtc att gac cgt gtg ctt aca caa att ggt acc tca att  | 722  |
| Val Val His Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile  |      |
| 225 230 235                                                      |      |
| caa gac ttc att gaa gca gaa gat gac ctt tca tct ttt aga gca gct  | 770  |
| Gln Asp Phe Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala  |      |
| 240 245 250                                                      |      |
| gcc atc aca tcg gac ata ttg gag gcc ctt gga aga gac ggt cac ttc  | 818  |
| Ala Ile Thr Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe  |      |
| 255 260 265                                                      |      |
| aca ctc ttt gct ccc acc aat gag gct ttt gag aaa ctt cca cga ggt  | 866  |
| Thr Leu Phe Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly  |      |
| 270 275 280 285                                                  |      |
| gtc cta gaa agg atc atg gga gac aaa gtg gct tcc gaa gct ctt atg  | 914  |
| Val Leu Glu Arg Ile Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met  |      |
| 290 295 300                                                      |      |
| aag tac cac atc tta aat act ctc cag tgt tct gag tct att atg gga  | 962  |
| Lys Tyr His Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly  |      |
| 305 310 315                                                      |      |
| gga gca gtc ttt gag acg ctg gaa gga aat aca att gag ata gga tgt  | 1010 |
| Gly Ala Val Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys  |      |
| 320 325 330                                                      |      |
| gac ggt gac agt ata aca gta aat gga atc aaa atg gtg aac aaa aag  | 1058 |
| Asp Gly Asp Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys  |      |
| 335 340 345                                                      |      |
| gat att gtg aca aat aat ggt gtg atc cat ttg att gat cag gtc cta  | 1106 |
| Asp Ile Val Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu  |      |
| 350 355 360 365                                                  |      |
| att cct gat tct gcc aaa caa gtt att gag ctg gct gga aaa cag caa  | 1154 |
| Ile Pro Asp Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln  |      |
| 370 375 380                                                      |      |
| acc acc ttc acg gat ctt gtg gcc caa tta ggc ttg gca tct gct ctg  | 1202 |
| Thr Thr Phe Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu  |      |
| 385 390 395                                                      |      |
| agg cca gat gga gaa tac act ttg ctg gca cct gtg aat aat gca ttt  | 1250 |
| Arg Pro Asp Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe  |      |
| 400 405 410                                                      |      |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| tct gat gat act ctc agc atg gat cag cgc ctc ctt aaa tta att ctg | 1298 |
| Ser Asp Asp Thr Leu Ser Met Asp Gln Arg Leu Leu Lys Leu Ile Leu |      |
| 415 420 425                                                     |      |
| cag aat cac ata ttg aaa gta aaa gtt ggc ctt aat gag ctt tac aac | 1346 |
| Gln Asn His Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn |      |
| 430 435 440 445                                                 |      |
| ggg caa ata ctg gaa acc atc gga ggc aaa cag ctc aga gtc ttc gta | 1394 |
| Gly Gln Ile Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val |      |
| 450 455 460                                                     |      |
| tat cgt aca gct gtc tgc att gaa aat tca tgc atg gag aaa ggg agt | 1442 |
| Tyr Arg Thr Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser |      |
| 465 470 475                                                     |      |
| aag caa ggg aga aac ggt gcg att cac ata ttc cgc gag atc atc aag | 1490 |
| Lys Gln Gly Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys |      |
| 480 485 490                                                     |      |
| cca gca gag aaa tcc ctc cat gaa aag tta aaa caa gat aag cgc ttt | 1538 |
| Pro Ala Glu Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe |      |
| 495 500 505                                                     |      |
| agc acc ttc ctc agc cta ctt gaa gct gca gac ttg aaa gag ctc ctg | 1586 |
| Ser Thr Phe Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu |      |
| 510 515 520 525                                                 |      |
| aca caa cct gga gac tgg aca tta ttt gtg cca acc aat gat gct ttt | 1634 |
| Thr Gln Pro Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe |      |
| 530 535 540                                                     |      |
| aag gga atg act agt gaa gaa aaa gaa att ctg ata cgg gac aaa aat | 1682 |
| Lys Gly Met Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn |      |
| 545 550 555                                                     |      |
| gct ctt caa aac atc att ctt tat cac ctg aca cca gga gtt ttc att | 1730 |
| Ala Leu Gln Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile |      |
| 560 565 570                                                     |      |
| gga aaa gga ttt gaa cct ggt gtt act aac att tta aag acc aca caa | 1778 |
| Gly Lys Gly Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln |      |
| 575 580 585                                                     |      |
| gga agc aaa atc ttt ctg aaa gaa gta aat gat aca ctt ctg gtg aat | 1826 |
| Gly Ser Lys Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn |      |
| 590 595 600 605                                                 |      |
| gaa ttg aaa tca aaa gaa tct gac atc atg aca aca aat ggt gta att | 1874 |
| Glu Leu Lys Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile |      |
| 610 615 620                                                     |      |
| cat gtt gta gat aaa ctc ctc tat cca gca gac aca cct gtt gga aat | 1922 |
| His Val Val Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn |      |
| 625 630 635                                                     |      |
| gat caa ctg ctg gaa ata ctt aat aaa tta atc aaa tac atc caa att | 1970 |
| Asp Gln Leu Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile |      |
| 640 645 650                                                     |      |
| aag ttt gtt cgt ggt agc acc ttc aaa gaa atc ccc gtg act gtc tat | 2018 |
| Lys Phe Val Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr |      |
| 655 660 665                                                     |      |
| agt cct gaa ata aaa tac act agg att tct act gga ggt gga gaa aca | 2066 |
| Ser Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr |      |
| 670 675 680 685                                                 |      |
| gaa gaa act ctg aag aaa ttg tta caa gaa gac aca ccc gtg agg aag | 2114 |
| Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Asp Thr Pro Val Arg Lys |      |
| 690 695 700                                                     |      |
| ttg caa gcc aac aaa aaa gtt caa ggt tct aga aga cga tta agg gaa | 2162 |
| Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu |      |
| 705 710 715                                                     |      |

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ggt cgt tct cag tga aaatccaaaa accagaaaaa aatgtttata caaccctaag 2217
Gly Arg Ser Gln *
720

tcaataaacct gaccttagaa aattgtgaga gccaaagtga cttcaggaac tgaaacatca 2277
gcacaaaagaa gcaatcatca aataattctg aacacaaatt taatattttt ttttctgaat 2337
gagaaacatg agggaaattg tggagttagc ctctgtggtt aaaggaattg aagaaaatat 2397
aacaccttac accctttttc atcttgacat taaaagttct ggctaacttt ggaatccatt 2457
agagaaaaat cctgtgcacc agattcatta caattcaaat cgaagagttg tgaactgtta 2517
tcccattgaa aagaccgagc cttgtatgta tggtatggat acataaaatg cagcaagcc 2577
attatctctc catgggaagc taagtataaa aaataggtgc ttggtgtaca aaacttttta 2637
tatcaaaagg ctttgcacat ttctatatga gtgggtttac tggtaaatta tgttattttt 2697
tacaactaat tttgtactct cagaatgttt gtcatatgct tcttgcaatg catatttttt 2757
aatctcaaac gtttcaataa aaccattttt cagatataaa gagaattact tcaaattgag 2817
taattcagaa aaactcaaga tttaagttaa aaagtggttt ggacttgga a 2868

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<210> SEQ ID NO 50
<211> LENGTH: 721
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 50

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Ile Val
1          5          10          15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20        25        30

Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35        40        45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50        55        60

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65        70        75        80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85        90        95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100       105       110

Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115       120       125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130       135       140

Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145       150       155       160

Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
165       170       175

Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
180       185       190

Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
195       200       205

Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His
210       215       220

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ile | Asp | Arg | Val | Leu | Thr | Gln | Ile | Gly | Thr | Ser | Ile | Gln | Asp | Phe |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Ile | Glu | Ala | Glu | Asp | Asp | Leu | Ser | Ser | Phe | Arg | Ala | Ala | Ala | Ile | Thr |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Ser | Asp | Ile | Leu | Glu | Ala | Leu | Gly | Arg | Asp | Gly | His | Phe | Thr | Leu | Phe |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ala | Pro | Thr | Asn | Glu | Ala | Phe | Glu | Lys | Leu | Pro | Arg | Gly | Val | Leu | Glu |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Arg | Ile | Met | Gly | Asp | Lys | Val | Ala | Ser | Glu | Ala | Leu | Met | Lys | Tyr | His |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Ile | Leu | Asn | Thr | Leu | Gln | Cys | Ser | Glu | Ser | Ile | Met | Gly | Gly | Ala | Val |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Phe | Glu | Thr | Leu | Glu | Gly | Asn | Thr | Ile | Glu | Ile | Gly | Cys | Asp | Gly | Asp |
|     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ser | Ile | Thr | Val | Asn | Gly | Ile | Lys | Met | Val | Asn | Lys | Lys | Asp | Ile | Val |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Thr | Asn | Asn | Gly | Val | Ile | His | Leu | Ile | Asp | Gln | Val | Leu | Ile | Pro | Asp |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Ser | Ala | Lys | Gln | Val | Ile | Glu | Leu | Ala | Gly | Lys | Gln | Gln | Thr | Thr | Phe |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Thr | Asp | Leu | Val | Ala | Gln | Leu | Gly | Leu | Ala | Ser | Ala | Leu | Arg | Pro | Asp |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Gly | Glu | Tyr | Thr | Leu | Leu | Ala | Pro | Val | Asn | Asn | Ala | Phe | Ser | Asp | Asp |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Thr | Leu | Ser | Met | Asp | Gln | Arg | Leu | Leu | Lys | Leu | Ile | Leu | Gln | Asn | His |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ile | Leu | Lys | Val | Lys | Val | Gly | Leu | Asn | Glu | Leu | Tyr | Asn | Gly | Gln | Ile |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Leu | Glu | Thr | Ile | Gly | Gly | Lys | Gln | Leu | Arg | Val | Phe | Val | Tyr | Arg | Thr |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Val | Cys | Ile | Glu | Asn | Ser | Cys | Met | Glu | Lys | Gly | Ser | Lys | Gln | Gly |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Arg | Asn | Gly | Ala | Ile | His | Ile | Phe | Arg | Glu | Ile | Ile | Lys | Pro | Ala | Glu |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Lys | Ser | Leu | His | Glu | Lys | Leu | Lys | Gln | Asp | Lys | Arg | Phe | Ser | Thr | Phe |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Leu | Ser | Leu | Leu | Glu | Ala | Ala | Asp | Leu | Lys | Glu | Leu | Leu | Thr | Gln | Pro |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Gly | Asp | Trp | Thr | Leu | Phe | Val | Pro | Thr | Asn | Asp | Ala | Phe | Lys | Gly | Met |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Thr | Ser | Glu | Glu | Lys | Glu | Ile | Leu | Ile | Arg | Asp | Lys | Asn | Ala | Leu | Gln |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Asn | Ile | Ile | Leu | Tyr | His | Leu | Thr | Pro | Gly | Val | Phe | Ile | Gly | Lys | Gly |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Phe | Glu | Pro | Gly | Val | Thr | Asn | Ile | Leu | Lys | Thr | Thr | Gln | Gly | Ser | Lys |
|     |     | 580 |     |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Ile | Phe | Leu | Lys | Glu | Val | Asn | Asp | Thr | Leu | Leu | Val | Asn | Glu | Leu | Lys |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Ser | Lys | Glu | Ser | Asp | Ile | Met | Thr | Thr | Asn | Gly | Val | Ile | His | Val | Val |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| Asp | Lys | Leu | Leu | Tyr | Pro | Ala | Asp | Thr | Pro | Val | Gly | Asn | Asp | Gln | Leu |

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| 625                                                              | 630 | 635             | 640 |     |
|------------------------------------------------------------------|-----|-----------------|-----|-----|
| Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val  | 645 | 650             | 655 |     |
| Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Ser Pro Glu  | 660 | 665             | 670 |     |
| Ile Lys Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr  | 675 | 680             | 685 |     |
| Leu Lys Lys Leu Leu Gln Glu Asp Thr Pro Val Arg Lys Leu Gln Ala  | 690 | 695             | 700 |     |
| Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser  | 705 | 710             | 715 | 720 |
| Gln                                                              |     |                 |     |     |
| <210> SEQ ID NO 51                                               |     |                 |     |     |
| <211> LENGTH: 576                                                |     |                 |     |     |
| <212> TYPE: DNA                                                  |     |                 |     |     |
| <213> ORGANISM: human                                            |     |                 |     |     |
| <220> FEATURE:                                                   |     |                 |     |     |
| <221> NAME/KEY: CDS                                              |     |                 |     |     |
| <222> LOCATION: (37) ... (477)                                   |     |                 |     |     |
| <400> SEQUENCE: 51                                               |     |                 |     |     |
| cttctctggg acacattgcc ttctgttttc tccagc atg cgc ttg ctc cag ctc  |     |                 |     | 54  |
|                                                                  |     | Met Arg Leu Leu | 5   |     |
| ctg ttc agg gcc agc cct gcc acc ctg ctc ctg gtt ctc tgc ctg cag  |     |                 |     | 102 |
| Leu Phe Arg Ala Ser Pro Ala Thr Leu Leu Leu Val Leu Cys Leu Gln  | 10  | 15              | 20  |     |
| ttg ggg gcc aac aaa gct cag gac aac act cgg aag atc ata ata aag  |     |                 |     | 150 |
| Leu Gly Ala Asn Lys Ala Gln Asp Asn Thr Arg Lys Ile Ile Ile Lys  | 25  | 30              | 35  |     |
| aat ttt gac att ccc aag tca gta cgt cca aat gac gaa gtc act gca  |     |                 |     | 198 |
| Asn Phe Asp Ile Pro Lys Ser Val Arg Pro Asn Asp Glu Val Thr Ala  | 40  | 45              | 50  |     |
| gtg ctt gca gtt caa aca gaa ttg aaa gaa tgc atg gtg gtt aaa act  |     |                 |     | 246 |
| Val Leu Ala Val Gln Thr Glu Leu Lys Glu Cys Met Val Val Lys Thr  | 55  | 60              | 65  | 70  |
| tac ctc att agc agc atc cct cta caa ggt gca ttt aac tat aag tat  |     |                 |     | 294 |
| Tyr Leu Ile Ser Ser Ile Pro Leu Gln Gly Ala Phe Asn Tyr Lys Tyr  | 75  | 80              | 85  |     |
| act gcc tgc cta tgt gac gac aat cca aaa acc ttc tac tgg gac ttt  |     |                 |     | 342 |
| Thr Ala Cys Leu Cys Asp Asp Asn Pro Lys Thr Phe Tyr Trp Asp Phe  | 90  | 95              | 100 |     |
| tac acc aac aga act gtg caa att gca gcc gtc gtt gat gtt att cgg  |     |                 |     | 390 |
| Tyr Thr Asn Arg Thr Val Gln Ile Ala Ala Val Val Asp Val Ile Arg  | 105 | 110             | 115 |     |
| gaa tta ggc atc tgc cct gat gat gct gct gta atc ccc atc aaa aac  |     |                 |     | 438 |
| Glu Leu Gly Ile Cys Pro Asp Asp Ala Ala Val Ile Pro Ile Lys Asn  | 120 | 125             | 130 |     |
| aac cgg ttt tat act att gaa atc cta aag gta gaa taa tggaagccct   |     |                 |     | 487 |
| Asn Arg Phe Tyr Thr Ile Glu Ile Leu Lys Val Glu *                | 135 | 140             | 145 |     |
| gtctgtttgc cacaccagg tgatttcctc taaagaaact tggttggaat ttctgctgtg |     |                 |     | 547 |
| gtctataaaa taaacttctt aacatgctt                                  |     |                 |     | 576 |
| <210> SEQ ID NO 52                                               |     |                 |     |     |

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<211> LENGTH: 146  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 52

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Met Arg Leu Leu Gln Leu Leu Phe Arg Ala Ser Pro Ala Thr Leu Leu
 1          5          10          15

Leu Val Leu Cys Leu Gln Leu Gly Ala Asn Lys Ala Gln Asp Asn Thr
 20          25          30

Arg Lys Ile Ile Ile Lys Asn Phe Asp Ile Pro Lys Ser Val Arg Pro
 35          40          45

Asn Asp Glu Val Thr Ala Val Leu Ala Val Gln Thr Glu Leu Lys Glu
 50          55          60

Cys Met Val Val Lys Thr Tyr Leu Ile Ser Ser Ile Pro Leu Gln Gly
 65          70          75          80

Ala Phe Asn Tyr Lys Tyr Thr Ala Cys Leu Cys Asp Asp Asn Pro Lys
 85          90          95

Thr Phe Tyr Trp Asp Phe Tyr Thr Asn Arg Thr Val Gln Ile Ala Ala
100          105          110

Val Val Asp Val Ile Arg Glu Leu Gly Ile Cys Pro Asp Asp Ala Ala
115          120          125

Val Ile Pro Ile Lys Asn Asn Arg Phe Tyr Thr Ile Glu Ile Leu Lys
130          135          140

Val Glu
145
  
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<210> SEQ ID NO 53  
 <211> LENGTH: 3734  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (81) ... (3077)

<400> SEQUENCE: 53

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ggcggtccgcg cacacctccc cgcgcgcgcg cgcgccaccgc ccgcaactccg ccgcctctgc      60

ccgcaaacgcg tgagccatccc atg ggg gtc gcg ggc cgc aac cgt ccc ggg gcg      113
      Met Gly Val Ala Gly Arg Asn Arg Pro Gly Ala
      1          5          10

gcc tgg gcg gtg ctg ctg ctg ctg ctg cta cca ctg ctg ctg ctg      161
Ala Trp Ala Val Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Leu
      15          20          25

gtg ggg gcc gtc ccg ccg ggt cgg ggc cgt gcc gcg ggg ccg cag gag      209
Val Gly Ala Val Pro Pro Gly Arg Gly Arg Ala Ala Gly Pro Gln Glu
      30          35          40

gat gta gat gag tgt gcc caa ggg cta gat gac tgc cat gcc gac gcc      257
Asp Val Asp Glu Cys Ala Gln Gly Leu Asp Asp Cys His Ala Asp Ala
      45          50          55

ctg tgt cag aac aca ccc acc tcc tac aag tgc tcc tgc aag cct ggc      305
Leu Cys Gln Asn Thr Pro Thr Ser Tyr Lys Cys Ser Cys Lys Pro Gly
      60          65          70          75

tac caa ggg gaa ggc agg cag tgt gag gac atc gat gaa tgt gga aat      353
Tyr Gln Gly Glu Gly Arg Gln Cys Glu Asp Ile Asp Glu Cys Gly Asn
      80          85          90

gag ctc aat gga ggc tgt gtc cat gac tgt ttg aat att cca ggc aat      401
Glu Leu Asn Gly Gly Cys Val His Asp Cys Leu Asn Ile Pro Gly Asn
      95          100          105
  
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|                                                                 |      |
|-----------------------------------------------------------------|------|
| tat cgt tgc act tgt ttt gat ggc ttc atg ttg gct cat gac ggt cat | 449  |
| Tyr Arg Cys Thr Cys Phe Asp Gly Phe Met Leu Ala His Asp Gly His |      |
| 110 115 120                                                     |      |
| aat tgt ctt gat gtg gac gag tgc ctg gag aac aat ggc ggc tgc cag | 497  |
| Asn Cys Leu Asp Val Asp Glu Cys Leu Glu Asn Asn Gly Gly Cys Gln |      |
| 125 130 135                                                     |      |
| cat acc tgt gtc aac gtc atg ggg agc tat gag tgc tgc tgc aag gag | 545  |
| His Thr Cys Val Asn Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu |      |
| 140 145 150 155                                                 |      |
| ggg ttt ttc ctg agt gac aat cag cac acc tgc att cac cgc tcg gaa | 593  |
| Gly Phe Phe Leu Ser Asp Asn Gln His Thr Cys Ile His Arg Ser Glu |      |
| 160 165 170                                                     |      |
| gag ggc ctg agc tgc atg aat aag gat cac ggc tgt agt cac atc tgc | 641  |
| Glu Gly Leu Ser Cys Met Asn Lys Asp His Gly Cys Ser His Ile Cys |      |
| 175 180 185                                                     |      |
| aag gag gcc cca agg ggc agc gtc gcc tgt gag tgc agg cct ggt ttt | 689  |
| Lys Glu Ala Pro Arg Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe |      |
| 190 195 200                                                     |      |
| gag ctg gcc aag aac cag aga gac tgc atc ttg acc tgt aac cat ggg | 737  |
| Glu Leu Ala Lys Asn Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly |      |
| 205 210 215                                                     |      |
| aac ggt ggg tgc cag cac tcc tgt gac gat aca gcc gat ggc cca gag | 785  |
| Asn Gly Gly Cys Gln His Ser Cys Asp Asp Thr Ala Asp Gly Pro Glu |      |
| 220 225 230 235                                                 |      |
| tgc agc tgc cat cca cag tac aag atg cac aca gat ggg agg agc tgc | 833  |
| Cys Ser Cys His Pro Gln Tyr Lys Met His Thr Asp Gly Arg Ser Cys |      |
| 240 245 250                                                     |      |
| ctt gag cga gag gac act gtc ctg gag gtg aca gag agc aac acc aca | 881  |
| Leu Glu Arg Glu Asp Thr Val Leu Glu Val Thr Glu Ser Asn Thr Thr |      |
| 255 260 265                                                     |      |
| tca gtg gtg gat ggg gat aaa cgg gtg aaa cgg cgg ctg ctc atg gaa | 929  |
| Ser Val Val Asp Gly Asp Lys Arg Val Lys Arg Arg Leu Leu Met Glu |      |
| 270 275 280                                                     |      |
| acg tgt gct gtc aac aat gga ggc tgt gac cgc acc tgt aag gat act | 977  |
| Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Arg Thr Cys Lys Asp Thr |      |
| 285 290 295                                                     |      |
| tcg aca ggt gtc cac tgc agt tgt cct gtt gga ttc act ctc cag ttg | 1025 |
| Ser Thr Gly Val His Cys Ser Cys Pro Val Gly Phe Thr Leu Gln Leu |      |
| 300 305 310 315                                                 |      |
| gat ggg aag aca tgt aaa gat att gat gag tgc cag acc cgc aat gga | 1073 |
| Asp Gly Lys Thr Cys Lys Asp Ile Asp Glu Cys Gln Thr Arg Asn Gly |      |
| 320 325 330                                                     |      |
| ggg tgt gat cat ttc tgc aaa aac atc gtg ggc agt ttt gac tgc ggc | 1121 |
| Gly Cys Asp His Phe Cys Lys Asn Ile Val Gly Ser Phe Asp Cys Gly |      |
| 335 340 345                                                     |      |
| tgc aag aaa gga ttt aaa tta tta aca gat gag aag tct tgc caa gat | 1169 |
| Cys Lys Lys Gly Phe Lys Leu Thr Asp Glu Lys Ser Cys Gln Asp     |      |
| 350 355 360                                                     |      |
| gtg gat gag tgc tct ttg gat agg acc tgt gac cac agc tgc atc aac | 1217 |
| Val Asp Glu Cys Ser Leu Asp Arg Thr Cys Asp His Ser Cys Ile Asn |      |
| 365 370 375                                                     |      |
| cac cct ggc aca ttt gct tgt gct tgc aac cga ggg tac acc ctg tat | 1265 |
| His Pro Gly Thr Phe Ala Cys Ala Cys Asn Arg Gly Tyr Thr Leu Tyr |      |
| 380 385 390 395                                                 |      |
| ggc ttc acc cac tgt gga gac acc aat gag tgc agc atc aac aac gga | 1313 |
| Gly Phe Thr His Cys Gly Asp Thr Asn Glu Cys Ser Ile Asn Asn Gly |      |
| 400 405 410                                                     |      |

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ggc tgt cag cag gtc tgt gtg aac aca gtg ggc agc tat gaa tgc cag<br>Gly Cys Gln Gln Val Cys Val Asn Thr Val Gly Ser Tyr Glu Cys Gln<br>415 420 425     | 1361 |
| tgc cac cct ggg tac aag ctc cac tgg aat aaa aaa gac tgt gtg gaa<br>Cys His Pro Gly Tyr Lys Leu His Trp Asn Lys Lys Asp Cys Val Glu<br>430 435 440     | 1409 |
| gtg aag ggg ctc ctg ccc aca agt gtg tca ccc cgt gtg tcc ctg cac<br>Val Lys Gly Leu Leu Pro Thr Ser Val Ser Pro Arg Val Ser Leu His<br>445 450 455     | 1457 |
| tgc ggt aag agt ggt gga gga gac ggg tgc ttc ctc aga tgt cac tct<br>Cys Gly Lys Ser Gly Gly Asp Gly Cys Phe Leu Arg Cys His Ser<br>460 465 470 475     | 1505 |
| ggc att cac ctc tct tca gat gtc acc acc atc agg aca agt gta acc<br>Gly Ile His Leu Ser Ser Asp Val Thr Thr Ile Arg Thr Ser Val Thr<br>480 485 490     | 1553 |
| ttt aag cta aat gaa ggc aag tgt agt ttg aaa aat gct gag ctg ttt<br>Phe Lys Leu Asn Glu Gly Lys Cys Ser Leu Lys Asn Ala Glu Leu Phe<br>495 500 505     | 1601 |
| ccc gag ggt ctg cga cca gca cta cca gag aag cac agc tca gta aaa<br>Pro Glu Gly Leu Arg Pro Ala Leu Pro Glu Lys His Ser Ser Val Lys<br>510 515 520     | 1649 |
| gag agc ttc cgc tac gta aac ctt aca tgc agc tct ggc aag caa gtc<br>Glu Ser Phe Arg Tyr Val Asn Leu Thr Cys Ser Ser Gly Lys Gln Val<br>525 530 535     | 1697 |
| cca gga gcc cct ggc cga cca agc acc cct aag gaa atg ttt atc act<br>Pro Gly Ala Pro Gly Arg Pro Ser Thr Pro Lys Glu Met Phe Ile Thr<br>540 545 550 555 | 1745 |
| gtt gag ttt gag ctt gaa act aac caa aag gag gtg aca gct tct tgt<br>Val Glu Phe Glu Leu Thr Asn Gln Lys Glu Val Thr Ala Ser Cys<br>560 565 570         | 1793 |
| gac ctg agc tgc atc gta aag cga acc gag aag cgg ctc cgt aaa gcc<br>Asp Leu Ser Cys Ile Val Lys Arg Thr Glu Lys Arg Leu Arg Lys Ala<br>575 580 585     | 1841 |
| atc cgc acg ctc aga aag gcc gtc cac agg gag cag ttt cac ctc cag<br>Ile Arg Thr Leu Arg Lys Ala Val His Arg Glu Gln Phe His Leu Gln<br>590 595 600     | 1889 |
| ctc tca ggc atg aac ctc gac gtg gct aaa aag cct ccc aga aca tct<br>Leu Ser Gly Met Asn Leu Asp Val Ala Lys Lys Pro Pro Arg Thr Ser<br>605 610 615     | 1937 |
| gaa cgc cag gca gag tcc tgt gga gtg ggc cag ggt cat gca gaa aac<br>Glu Arg Gln Ala Glu Ser Cys Gly Val Gly Gln Gly His Ala Glu Asn<br>620 625 630 635 | 1985 |
| caa tgt gtc agt tgc agg gct ggg acc tat tat gat gga gca cga gaa<br>Gln Cys Val Ser Cys Arg Ala Gly Thr Tyr Asp Gly Ala Arg Glu<br>640 645 650         | 2033 |
| cgc tgc att tta tgt cca aat gga acc ttc caa aat gag gaa gga caa<br>Arg Cys Ile Leu Cys Pro Asn Gly Thr Phe Gln Asn Glu Glu Gly Gln<br>655 660 665     | 2081 |
| atg act tgt gaa cca tgc cca aga cca gga aat tct ggg gcc ctg aag<br>Met Thr Cys Glu Pro Cys Pro Arg Pro Gly Asn Ser Gly Ala Leu Lys<br>670 675 680     | 2129 |
| acc cca gaa gct tgg aat atg tct gaa tgt gga ggt ctg tgt caa cct<br>Thr Pro Glu Ala Trp Asn Met Ser Glu Cys Gly Gly Leu Cys Gln Pro<br>685 690 695     | 2177 |
| ggg gaa tat tct gca gat ggc ttt gca cct tgc cag ctc tgt gcc ctg<br>Gly Glu Tyr Ser Ala Asp Gly Phe Ala Pro Cys Gln Leu Cys Ala Leu<br>700 705 710 715 | 2225 |

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ggc acg ttc cag cct gaa gct ggt cga act tcc tgc ttc ccc tgt gga<br>Gly Thr Phe Gln Pro Glu Ala Gly Arg Thr Ser Cys Phe Pro Cys Gly<br>720 725 730     | 2273 |
| gga ggc ctt gcc acc aaa cat cag gga gct act tcc ttt cag gac tgt<br>Gly Gly Leu Ala Thr Lys His Gln Gly Ala Thr Ser Phe Gln Asp Cys<br>735 740 745     | 2321 |
| gaa acc aga gtt caa tgt tca cct gga cat ttc tac aac acc acc act<br>Glu Thr Arg Val Gln Cys Ser Pro Gly His Phe Tyr Asn Thr Thr Thr<br>750 755 760     | 2369 |
| cac cga tgt att cgt tgc cca gtg gga aca tac cag cct gaa ttt gga<br>His Arg Cys Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe Gly<br>765 770 775     | 2417 |
| aaa aat aat tgt gtt tct tgc cca gga aat act acg act gac ttt gat<br>Lys Asn Asn Cys Val Ser Cys Pro Gly Asn Thr Thr Thr Asp Phe Asp<br>780 785 790 795 | 2465 |
| ggc tcc aca aac ata acc cag tgt aaa aac aga aga tgt gga ggg gag<br>Gly Ser Thr Asn Ile Thr Gln Cys Lys Asn Arg Arg Cys Gly Gly Glu<br>800 805 810     | 2513 |
| ctg gga gat ttc act ggg tac att gaa tcc cca aac tac cca ggc aat<br>Leu Gly Asp Phe Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly Asn<br>815 820 825     | 2561 |
| tac cca gcc aac acc gag tgt acg tgg acc atc aac cca ccc ccc aag<br>Tyr Pro Ala Asn Thr Glu Cys Thr Trp Thr Ile Asn Pro Pro Pro Lys<br>830 835 840     | 2609 |
| cgc cgc atc ctg atc gtg gtc cct gag atc ttc ctg ccc ata gag gac<br>Arg Arg Ile Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu Asp<br>845 850 855     | 2657 |
| gac tgt ggg gac tat ctg gtg atg cgg aaa acc tct tca tcc aat tct<br>Asp Cys Gly Asp Tyr Leu Val Met Arg Lys Thr Ser Ser Ser Asn Ser<br>860 865 870 875 | 2705 |
| gtg aca aca tat gaa acc tgc cag acc tac gaa cgc ccc atc gcc ttc<br>Val Thr Thr Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala Phe<br>880 885 890     | 2753 |
| acc tcc agg tca aag aag ctg tgg att cag ttc aag tcc aat gaa ggg<br>Thr Ser Arg Ser Lys Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu Gly<br>895 900 905     | 2801 |
| aac agc gct aga ggg ttc cag gtc cca tac gtg aca tat gat gag gac<br>Asn Ser Ala Arg Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Glu Asp<br>910 915 920     | 2849 |
| tac cag gaa ctc att gaa gac ata gtt cga gat ggc agg ctc tat gca<br>Tyr Gln Glu Leu Ile Glu Asp Ile Val Arg Asp Gly Arg Leu Tyr Ala<br>925 930 935     | 2897 |
| tct gag aac cat cag gaa ata ctt aag gat aag aaa ctt atc aag gct<br>Ser Glu Asn His Gln Glu Ile Leu Lys Asp Lys Lys Leu Ile Lys Ala<br>940 945 950 955 | 2945 |
| ctg ttt gat gtc ctg gcc cat ccc cag aac tat ttc aag tac aca gcc<br>Leu Phe Asp Val Leu Ala His Pro Gln Asn Tyr Phe Lys Tyr Thr Ala<br>960 965 970     | 2993 |
| cag gag tcc cga gag atg ttt cca aga tcg ttc atc cga ttg cta cgt<br>Gln Glu Ser Arg Glu Met Phe Pro Arg Ser Phe Ile Arg Leu Leu Arg<br>975 980 985     | 3041 |
| tcc aaa gtg tcc agg ttt ttg aga cct tac aaa tga ctccagccac<br>Ser Lys Val Ser Arg Phe Leu Arg Pro Tyr Lys *                                           | 3087 |
| 990 995                                                                                                                                               |      |
| gtgccactca atacaaatgt tctgctatag gggtggtggg acagagctgt cttccttctg                                                                                     | 3147 |
| catgtcagca cagtcgggta ttgctgcttc ccgtatcagt gactcattag agttcaattt                                                                                     | 3207 |

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ttatagataa tacagatatt ttggtaaatt gaacttggtt tttctttccc agcatcgtgg 3267
atgtagactg agaatggcct tgagtggcat cagctttctca ctgctgtggg cggatgtctt 3327
ggatagatca cgggctggct gagctggact ttggtcagcc taggtgagac tcacctgtcc 3387
ttctggggtc ttactcctcc tcaaggagtc tgtagtggaa aggaggccac agaataagct 3447
gcttattctg aaacttcagc ttcctctagc cgggccctct ctaagggagc cctctgcact 3507
cgtgtgcagg ctctgaccag gcagaacagg caagagggga ggaaggaga cccctgcagg 3567
ctccctccac ccaccttgag acctgggagg actcagtttc tccacagcct tctccagcct 3627
gtgtgataca agtttgatcc caggaacttg agttctaagc agtgctcgtg aaaaaaaaaa 3687
gcagaaagaa ttagaaataa ataaaaacta agcacttctg gagacat 3734

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&lt;210&gt; SEQ ID NO 54

&lt;211&gt; LENGTH: 998

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 54

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Met Gly Val Ala Gly Arg Asn Arg Pro Gly Ala Ala Trp Ala Val Leu
1           5           10          15
Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Leu Val Gly Ala Val Pro
20          25          30
Pro Gly Arg Gly Arg Ala Ala Gly Pro Gln Glu Asp Val Asp Glu Cys
35          40          45
Ala Gln Gly Leu Asp Asp Cys His Ala Asp Ala Leu Cys Gln Asn Thr
50          55          60
Pro Thr Ser Tyr Lys Cys Ser Cys Lys Pro Gly Tyr Gln Gly Glu Gly
65          70          75          80
Arg Gln Cys Glu Asp Ile Asp Glu Cys Gly Asn Glu Leu Asn Gly Gly
85          90          95
Cys Val His Asp Cys Leu Asn Ile Pro Gly Asn Tyr Arg Cys Thr Cys
100         105         110
Phe Asp Gly Phe Met Leu Ala His Asp Gly His Asn Cys Leu Asp Val
115         120         125
Asp Glu Cys Leu Glu Asn Asn Gly Gly Cys Gln His Thr Cys Val Asn
130         135         140
Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu Gly Phe Phe Leu Ser
145         150         155         160
Asp Asn Gln His Thr Cys Ile His Arg Ser Glu Glu Gly Leu Ser Cys
165         170         175
Met Asn Lys Asp His Gly Cys Ser His Ile Cys Lys Glu Ala Pro Arg
180         185         190
Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Ala Lys Asn
195         200         205
Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly Asn Gly Gly Cys Gln
210         215         220
His Ser Cys Asp Asp Thr Ala Asp Gly Pro Glu Cys Ser Cys His Pro
225         230         235         240
Gln Tyr Lys Met His Thr Asp Gly Arg Ser Cys Leu Glu Arg Glu Asp
245         250         255
Thr Val Leu Glu Val Thr Glu Ser Asn Thr Thr Ser Val Val Asp Gly

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| 260 |     |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Asp | Lys | Arg | Val | Lys | Arg | Arg | Leu | Leu | Met | Glu | Thr | Cys | Ala | Val | Asn |  |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| Asn | Gly | Gly | Cys | Asp | Arg | Thr | Cys | Lys | Asp | Thr | Ser | Thr | Gly | Val | His |  |
|     |     | 290 |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| Cys | Ser | Cys | Pro | Val | Gly | Phe | Thr | Leu | Gln | Leu | Asp | Gly | Lys | Thr | Cys |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| Lys | Asp | Ile | Asp | Glu | Cys | Gln | Thr | Arg | Asn | Gly | Gly | Cys | Asp | His | Phe |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| Cys | Lys | Asn | Ile | Val | Gly | Ser | Phe | Asp | Cys | Gly | Cys | Lys | Lys | Gly | Phe |  |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
| Lys | Leu | Leu | Thr | Asp | Glu | Lys | Ser | Cys | Gln | Asp | Val | Asp | Glu | Cys | Ser |  |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
| Leu | Asp | Arg | Thr | Cys | Asp | His | Ser | Cys | Ile | Asn | His | Pro | Gly | Thr | Phe |  |
|     |     | 370 |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
| Ala | Cys | Ala | Cys | Asn | Arg | Gly | Tyr | Thr | Leu | Tyr | Gly | Phe | Thr | His | Cys |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
| Gly | Asp | Thr | Asn | Glu | Cys | Ser | Ile | Asn | Asn | Gly | Gly | Cys | Gln | Gln | Val |  |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| Cys | Val | Asn | Thr | Val | Gly | Ser | Tyr | Glu | Cys | Gln | Cys | His | Pro | Gly | Tyr |  |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
| Lys | Leu | His | Trp | Asn | Lys | Lys | Asp | Cys | Val | Glu | Val | Lys | Gly | Leu | Leu |  |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
| Pro | Thr | Ser | Val | Ser | Pro | Arg | Val | Ser | Leu | His | Cys | Gly | Lys | Ser | Gly |  |
|     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| Gly | Gly | Asp | Gly | Cys | Phe | Leu | Arg | Cys | His | Ser | Gly | Ile | His | Leu | Ser |  |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
| Ser | Asp | Val | Thr | Thr | Ile | Arg | Thr | Ser | Val | Thr | Phe | Lys | Leu | Asn | Glu |  |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
| Gly | Lys | Cys | Ser | Leu | Lys | Asn | Ala | Glu | Leu | Phe | Pro | Glu | Gly | Leu | Arg |  |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |
| Pro | Ala | Leu | Pro | Glu | Lys | His | Ser | Ser | Val | Lys | Glu | Ser | Phe | Arg | Tyr |  |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
| Val | Asn | Leu | Thr | Cys | Ser | Ser | Gly | Lys | Gln | Val | Pro | Gly | Ala | Pro | Gly |  |
|     |     | 530 |     |     |     |     | 535 |     |     |     | 540 |     |     |     |     |  |
| Arg | Pro | Ser | Thr | Pro | Lys | Glu | Met | Phe | Ile | Thr | Val | Glu | Phe | Glu | Leu |  |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |
| Glu | Thr | Asn | Gln | Lys | Glu | Val | Thr | Ala | Ser | Cys | Asp | Leu | Ser | Cys | Ile |  |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |
| Val | Lys | Arg | Thr | Glu | Lys | Arg | Leu | Arg | Lys | Ala | Ile | Arg | Thr | Leu | Arg |  |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |
| Lys | Ala | Val | His | Arg | Glu | Gln | Phe | His | Leu | Gln | Leu | Ser | Gly | Met | Asn |  |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
| Leu | Asp | Val | Ala | Lys | Lys | Pro | Pro | Arg | Thr | Ser | Glu | Arg | Gln | Ala | Glu |  |
|     |     | 610 |     |     |     |     | 615 |     |     |     | 620 |     |     |     |     |  |
| Ser | Cys | Gly | Val | Gly | Gln | Gly | His | Ala | Glu | Asn | Gln | Cys | Val | Ser | Cys |  |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |  |
| Arg | Ala | Gly | Thr | Tyr | Tyr | Asp | Gly | Ala | Arg | Glu | Arg | Cys | Ile | Leu | Cys |  |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |  |
| Pro | Asn | Gly | Thr | Phe | Gln | Asn | Glu | Glu | Gly | Gln | Met | Thr | Cys | Glu | Pro |  |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |  |

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Cys Pro Arg Pro Gly Asn Ser Gly Ala Leu Lys Thr Pro Glu Ala Trp  
 675 680 685  
 Asn Met Ser Glu Cys Gly Gly Leu Cys Gln Pro Gly Glu Tyr Ser Ala  
 690 695 700  
 Asp Gly Phe Ala Pro Cys Gln Leu Cys Ala Leu Gly Thr Phe Gln Pro  
 705 710 715 720  
 Glu Ala Gly Arg Thr Ser Cys Phe Pro Cys Gly Gly Gly Leu Ala Thr  
 725 730 735  
 Lys His Gln Gly Ala Thr Ser Phe Gln Asp Cys Glu Thr Arg Val Gln  
 740 745 750  
 Cys Ser Pro Gly His Phe Tyr Asn Thr Thr Thr His Arg Cys Ile Arg  
 755 760 765  
 Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe Gly Lys Asn Asn Cys Val  
 770 775 780  
 Ser Cys Pro Gly Asn Thr Thr Thr Asp Phe Asp Gly Ser Thr Asn Ile  
 785 790 795 800  
 Thr Gln Cys Lys Asn Arg Arg Cys Gly Gly Glu Leu Gly Asp Phe Thr  
 805 810 815  
 Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala Asn Thr  
 820 825 830  
 Glu Cys Thr Trp Thr Ile Asn Pro Pro Pro Lys Arg Arg Ile Leu Ile  
 835 840 845  
 Val Val Pro Glu Ile Phe Leu Pro Ile Glu Asp Asp Cys Gly Asp Tyr  
 850 855 860  
 Leu Val Met Arg Lys Thr Ser Ser Ser Asn Ser Val Thr Thr Tyr Glu  
 865 870 875 880  
 Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala Phe Thr Ser Arg Ser Lys  
 885 890 895  
 Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu Gly Asn Ser Ala Arg Gly  
 900 905 910  
 Phe Gln Val Pro Tyr Val Thr Tyr Asp Glu Asp Tyr Gln Glu Leu Ile  
 915 920 925  
 Glu Asp Ile Val Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His Gln  
 930 935 940  
 Glu Ile Leu Lys Asp Lys Lys Leu Ile Lys Ala Leu Phe Asp Val Leu  
 945 950 955 960  
 Ala His Pro Gln Asn Tyr Phe Lys Tyr Thr Ala Gln Glu Ser Arg Glu  
 965 970 975  
 Met Phe Pro Arg Ser Phe Ile Arg Leu Leu Arg Ser Lys Val Ser Arg  
 980 985 990  
 Phe Leu Arg Pro Tyr Lys  
 995

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 <212> TYPE: DNA  
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|                                                                    |     |
|--------------------------------------------------------------------|-----|
| ccgcaaccgc tgaagccatcc atg ggg gtc gcg ggc cgc aac cgt ccc ggg gcg | 113 |
| Met Gly Val Ala Gly Arg Asn Arg Pro Gly Ala                        |     |
| 1 5 10                                                             |     |
| gcc tgg gcg gtg ctg ctg ctg ctg ctg cta cca ctg ctg ctg ctg        | 161 |
| Ala Trp Ala Val Leu Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Leu    |     |
| 15 20 25                                                           |     |
| gtg ggg gcc gtc ccg ccg ggt cgg ggc cgt gcc gcg ggg ccg cag gag    | 209 |
| Val Gly Ala Val Pro Pro Gly Arg Gly Arg Ala Ala Gly Pro Gln Glu    |     |
| 30 35 40                                                           |     |
| gat gta gat gag tgt gcc caa ggg cta gat gac tgc cat gcc gac gcc    | 257 |
| Asp Val Asp Glu Cys Ala Gln Gly Leu Asp Asp Cys His Ala Asp Ala    |     |
| 45 50 55                                                           |     |
| ctg tgt cag aac aca ccc acc tcc tac aag tgc tcc tgc aag cct ggc    | 305 |
| Leu Cys Gln Asn Thr Pro Thr Ser Tyr Lys Cys Ser Cys Lys Pro Gly    |     |
| 60 65 70 75                                                        |     |
| tac caa ggg gaa ggc agg cag tgt gag gac atc gat gaa tgt gga aat    | 353 |
| Tyr Gln Gly Glu Gly Arg Gln Cys Glu Asp Ile Asp Glu Cys Gly Asn    |     |
| 80 85 90                                                           |     |
| gag ctc aat gga ggc tgt gtc cat gac tgt ttg aat att cca ggc aat    | 401 |
| Glu Leu Asn Gly Gly Cys Val His Asp Cys Leu Asn Ile Pro Gly Asn    |     |
| 95 100 105                                                         |     |
| tat cgt tgc act tgt ttt gat ggc ttc atg ttg gct cat gac ggt cat    | 449 |
| Tyr Arg Cys Thr Cys Phe Asp Gly Phe Met Leu Ala His Asp Gly His    |     |
| 110 115 120                                                        |     |
| aat tgt ctt gat gtg gac gag tgc ctg gag aac aat ggc ggc tgc cag    | 497 |
| Asn Cys Leu Asp Val Asp Glu Cys Leu Glu Asn Asn Gly Gly Cys Gln    |     |
| 125 130 135                                                        |     |
| cat acc tgt gtc aac gtc atg ggg agc tat gag tgc tgc tgc aag gag    | 545 |
| His Thr Cys Val Asn Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu    |     |
| 140 145 150 155                                                    |     |
| ggg ttt ttc ctg agt gac aat cag cac acc tgc att cac cgc tcg gaa    | 593 |
| Gly Phe Phe Leu Ser Asp Asn Gln His Thr Cys Ile His Arg Ser Glu    |     |
| 160 165 170                                                        |     |
| gag ggc ctg agc tgc atg aat aag gat cac ggc tgt agt cac atc tgc    | 641 |
| Glu Gly Leu Ser Cys Met Asn Lys Asp His Gly Cys Ser His Ile Cys    |     |
| 175 180 185                                                        |     |
| aag gag gcc cca agg ggc agc gtc gcc tgt gag tgc agg cct ggt ttt    | 689 |
| Lys Glu Ala Pro Arg Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe    |     |
| 190 195 200                                                        |     |
| gag ctg gcc aag aac cag aga gac tgc atc ttg acc tgt aac cat ggg    | 737 |
| Glu Leu Ala Lys Asn Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly    |     |
| 205 210 215                                                        |     |
| aac ggt ggg tgc cag cac tcc tgt gac gat aca gcc gat ggc cca gag    | 785 |
| Asn Gly Gly Cys Gln His Ser Cys Asp Asp Thr Ala Asp Gly Pro Glu    |     |
| 220 225 230 235                                                    |     |
| tgc agc tgc cat cca cag tac aag atg cac aca gat ggg agg agc tgc    | 833 |
| Cys Ser Cys His Pro Gln Tyr Lys Met His Thr Asp Gly Arg Ser Cys    |     |
| 240 245 250                                                        |     |
| ctt gag cga gag gac act gtc ctg gag gtg aca gag agc aac acc aca    | 881 |
| Leu Glu Arg Glu Asp Thr Val Leu Glu Val Thr Glu Ser Asn Thr Thr    |     |
| 255 260 265                                                        |     |
| tca gtg gtg gat ggg gat aaa cgg gtg aaa cgg cgg ctg ctc atg gaa    | 929 |
| Ser Val Val Asp Gly Asp Lys Arg Val Lys Arg Arg Leu Leu Met Glu    |     |
| 270 275 280                                                        |     |
| acg tgt gct gtc aac aat gga ggc tgt gac cgc acc tgt aag gat act    | 977 |
| Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Arg Thr Cys Lys Asp Thr    |     |
| 285 290 295                                                        |     |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| tcg aca ggt gtc cac tgc agt tgt cct gtt gga ttc act ctc cag ttg | 1025 |
| Ser Thr Gly Val His Cys Ser Cys Pro Val Gly Phe Thr Leu Gln Leu |      |
| 300 305 310 315                                                 |      |
| gat ggg aag aca tgt aaa gat att gat gag tgc cag acc cgc aat gga | 1073 |
| Asp Gly Lys Thr Cys Lys Asp Ile Asp Glu Cys Gln Thr Arg Asn Gly |      |
| 320 325 330                                                     |      |
| ggg tgt gat cat ttc tgc aaa aac atc gtg ggc agt ttt gac tgc ggc | 1121 |
| Gly Cys Asp His Phe Cys Lys Asn Ile Val Gly Ser Phe Asp Cys Gly |      |
| 335 340 345                                                     |      |
| tgc aag aaa gga ttt aaa tta tta aca gat gag aag tct tgc caa gat | 1169 |
| Cys Lys Lys Gly Phe Lys Leu Leu Thr Asp Glu Lys Ser Cys Gln Asp |      |
| 350 355 360                                                     |      |
| gtg gat gag tgc tct ttg gat agg acc tgt gac cac agc tgc atc aac | 1217 |
| Val Asp Glu Cys Ser Leu Asp Arg Thr Cys Asp His Ser Cys Ile Asn |      |
| 365 370 375                                                     |      |
| cac cct ggc aca ttt gct tgt gct tgc aac cga ggg tac acc ctg tat | 1265 |
| His Pro Gly Thr Phe Ala Cys Ala Cys Asn Arg Gly Tyr Thr Leu Tyr |      |
| 380 385 390 395                                                 |      |
| ggc ttc acc cac tgt gga gat gtc acc acc atc agg aca agt gta acc | 1313 |
| Gly Phe Thr His Cys Gly Asp Val Thr Thr Ile Arg Thr Ser Val Thr |      |
| 400 405 410                                                     |      |
| ttt aag cta aat gaa ggc aag tgt agt ttg aaa aat gct gag ctg ttt | 1361 |
| Phe Lys Leu Asn Glu Gly Lys Cys Ser Leu Lys Asn Ala Glu Leu Phe |      |
| 415 420 425                                                     |      |
| ccc gag ggt ctg cga cca gca cta cca gag aag cac agc tca gta aaa | 1409 |
| Pro Glu Gly Leu Arg Pro Ala Leu Pro Glu Lys His Ser Ser Val Lys |      |
| 430 435 440                                                     |      |
| gag agc ttc cgc tac gta aac ctt aca tgc agc tct ggc aag caa gtc | 1457 |
| Glu Ser Phe Arg Tyr Val Asn Leu Thr Cys Ser Ser Gly Lys Gln Val |      |
| 445 450 455                                                     |      |
| cca gga gcc cct ggc cga cca agc acc cct aag gaa atg ttt atc act | 1505 |
| Pro Gly Ala Pro Gly Arg Pro Ser Thr Pro Lys Glu Met Phe Ile Thr |      |
| 460 465 470 475                                                 |      |
| gtt gag ttt gag ctt gaa act aac caa aag gag gtg aca gct tct tgt | 1553 |
| Val Glu Phe Glu Leu Glu Thr Asn Gln Lys Glu Val Thr Ala Ser Cys |      |
| 480 485 490                                                     |      |
| gac ctg agc tgc atc gta aag cga acc gag aag cgg ctc cgt aaa gcc | 1601 |
| Asp Leu Ser Cys Ile Val Lys Arg Thr Glu Lys Arg Leu Arg Lys Ala |      |
| 495 500 505                                                     |      |
| atc cgc acg ctc aga aag gcc gtc cac agg gag cag ttt cac ctc cag | 1649 |
| Ile Arg Thr Leu Arg Lys Ala Val His Arg Glu Gln Phe His Leu Gln |      |
| 510 515 520                                                     |      |
| ctc tca ggc atg aac ctc gac gtg gct aaa aag cct ccc aga aca tct | 1697 |
| Leu Ser Gly Met Asn Leu Asp Val Ala Lys Lys Pro Pro Arg Thr Ser |      |
| 525 530 535                                                     |      |
| gaa cgc cag gca gag tcc tgt gga gtg ggc cag ggt cat gca gaa aac | 1745 |
| Glu Arg Gln Ala Glu Ser Cys Gly Val Gly Gln Gly His Ala Glu Asn |      |
| 540 545 550 555                                                 |      |
| caa tgt gtc agt tgc agg gct ggg acc tat tat gat gga gca cga gaa | 1793 |
| Gln Cys Val Ser Cys Arg Ala Gly Thr Tyr Tyr Asp Gly Ala Arg Glu |      |
| 560 565 570                                                     |      |
| cgc tgc att tta tgt cca aat gga acc ttc caa aat gag gaa gga caa | 1841 |
| Arg Cys Ile Leu Cys Pro Asn Gly Thr Phe Gln Asn Glu Glu Gly Gln |      |
| 575 580 585                                                     |      |
| atg act tgt gaa cca tgc cca aga cca gga aat tct ggg gcc ctg aag | 1889 |
| Met Thr Cys Glu Pro Cys Pro Arg Pro Gly Asn Ser Gly Ala Leu Lys |      |
| 590 595 600                                                     |      |

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| acc cca gaa gct tgg aat atg tct gaa tgt gga ggt ctg tgt caa cct<br>Thr Pro Glu Ala Trp Asn Met Ser Glu Cys Gly Gly Leu Cys Gln Pro<br>605 610 615     | 1937 |
| ggt gaa tat tct gca gat ggc ttt gca cct tgc cag ctc tgt gcc ctg<br>Gly Glu Tyr Ser Ala Asp Gly Phe Ala Pro Cys Gln Leu Cys Ala Leu<br>620 625 630 635 | 1985 |
| ggc acg ttc cag cct gaa gct ggt cga act tcc tgc ttc ccc tgt gga<br>Gly Thr Phe Gln Pro Glu Ala Gly Arg Thr Ser Cys Phe Pro Cys Gly<br>640 645 650     | 2033 |
| gga ggc ctt gcc acc aaa cat cag gga gct act tcc ttt cag gac tgt<br>Gly Gly Leu Ala Thr Lys His Gln Gly Ala Thr Ser Phe Gln Asp Cys<br>655 660 665     | 2081 |
| gaa acc aga gtt caa tgt tca cct gga cat ttc tac aac acc acc act<br>Glu Thr Arg Val Gln Cys Ser Pro Gly His Phe Tyr Asn Thr Thr Thr<br>670 675 680     | 2129 |
| cac cga tgt att cgt tgc cca gtg gga aca tac cag cct gaa ttt gga<br>His Arg Cys Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe Gly<br>685 690 695     | 2177 |
| aaa aat aat tgt gtt tct tgc cca gga aat act acg act gac ttt gat<br>Lys Asn Asn Cys Val Ser Cys Pro Gly Asn Thr Thr Thr Asp Phe Asp<br>700 705 710 715 | 2225 |
| ggc tcc aca aac ata acc cag tgt aaa aac aga aga tgt gga ggg gag<br>Gly Ser Thr Asn Ile Thr Gln Cys Lys Asn Arg Arg Cys Gly Gly Glu<br>720 725 730     | 2273 |
| ctg gga gat ttc act ggg tac att gaa tcc cca aac tac cca ggc aat<br>Leu Gly Asp Phe Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly Asn<br>735 740 745     | 2321 |
| tac cca gcc aac acc gag tgt acg tgg acc atc aac cca ccc ccc aag<br>Tyr Pro Ala Asn Thr Glu Cys Thr Trp Thr Ile Asn Pro Pro Pro Lys<br>750 755 760     | 2369 |
| cgc cgc atc ctg atc gtg gtc cct gag atc ttc ctg ccc ata gag gac<br>Arg Arg Ile Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu Asp<br>765 770 775     | 2417 |
| gac tgt ggg gac tat ctg gtg atg cgg aaa acc tct tca tcc aat tct<br>Asp Cys Gly Asp Tyr Leu Val Met Arg Lys Thr Ser Ser Ser Asn Ser<br>780 785 790 795 | 2465 |
| gtg aca aca tat gaa acc tgc cag acc tac gaa cgc ccc atc gcc ttc<br>Val Thr Thr Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala Phe<br>800 805 810     | 2513 |
| acc tcc agg tca aag aag ctg tgg att cag ttc aag tcc aat gaa ggg<br>Thr Ser Arg Ser Lys Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu Gly<br>815 820 825     | 2561 |
| aac agc gct aga ggg ttc cag gtc cca tac gtg aca tat gat gag gac<br>Asn Ser Ala Arg Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Glu Asp<br>830 835 840     | 2609 |
| tac cag gaa ctc att gaa gac ata gtt cga gat ggc agg ctc tat gca<br>Tyr Gln Glu Leu Ile Glu Asp Ile Val Arg Asp Gly Arg Leu Tyr Ala<br>845 850 855     | 2657 |
| tct gag aac cat cag gaa ata ctt aag gat aag aaa ctt atc aag gct<br>Ser Glu Asn His Gln Glu Ile Leu Lys Asp Lys Lys Leu Ile Lys Ala<br>860 865 870 875 | 2705 |
| ctg ttt gat gtc ctg gcc cat ccc cag aac tat ttc aag tac aca gcc<br>Leu Phe Asp Val Leu Ala His Pro Gln Asn Tyr Phe Lys Tyr Thr Ala<br>880 885 890     | 2753 |
| cag gag tcc cga gag atg ttt cca aga tgc ttc atc cga ttg cta cgt<br>Gln Glu Ser Arg Glu Met Phe Pro Arg Ser Phe Ile Arg Leu Leu Arg<br>895 900 905     | 2801 |

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tcc aaa gtg tcc agg ttt ttg aga cct tac aaa tga ctcagcccac      2847
Ser Lys Val Ser Arg Phe Leu Arg Pro Tyr Lys  *
      910                      915

gtgccactca atacaaatgt tctgctatag gggtggtggg acagagctgt cttccttctg  2907
catgtcagca cagtcgggta ttgctgcctc ccgtatcagt gactcattag agttcaattt  2967
ttatagataa tacagatatt ttggtaaatt gaacttggtt tttctttccc agcatcgtgg  3027
atgtagactg agaatggctt tgagtggcat cagcttctca ctgctgtggg cggatgtctt  3087
ggatagatca cgggctggct gagctggact ttggtcagcc taggtgagac tcacctgtcc  3147
ttctggggtc ttactcctcc tcaaggagtc tgtagtggaaggaggccac agaataagct  3207
gcttattctg aaacttcagc ttcctctagc ccggccctct ctaagggagc cctctgcact  3267
cgtgtgcagg ctctgaccag gcagaacagg caagagggga gggaaggaga cccctgcagg  3327
ctccctccac ccacctgtag acctgggagg actcagtttc tccacagcct tctccagcct  3387
gtgtgataca agtttgatcc caggaacttg agttctaagc agtgctcgtg aaaaaaaaaa  3447
gcagaaagaa ttagaaataa ataaaaacta agcacttctg gagacat                3494

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<210> SEQ ID NO 56
<211> LENGTH: 918
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 56

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Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Val Gly Ala Val Pro
      20              25              30

Pro Gly Arg Gly Arg Ala Ala Gly Pro Gln Glu Asp Val Asp Glu Cys
      35              40              45

Ala Gln Gly Leu Asp Asp Cys His Ala Asp Ala Leu Cys Gln Asn Thr
      50              55              60

Pro Thr Ser Tyr Lys Cys Ser Cys Lys Pro Gly Tyr Gln Gly Glu Gly
      65              70              75              80

Arg Gln Cys Glu Asp Ile Asp Glu Cys Gly Asn Glu Leu Asn Gly Gly
      85              90              95

Cys Val His Asp Cys Leu Asn Ile Pro Gly Asn Tyr Arg Cys Thr Cys
      100             105             110

Phe Asp Gly Phe Met Leu Ala His Asp Gly His Asn Cys Leu Asp Val
      115             120             125

Asp Glu Cys Leu Glu Asn Asn Gly Gly Cys Gln His Thr Cys Val Asn
      130             135             140

Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu Gly Phe Phe Leu Ser
      145             150             155             160

Asp Asn Gln His Thr Cys Ile His Arg Ser Glu Glu Gly Leu Ser Cys
      165             170             175

Met Asn Lys Asp His Gly Cys Ser His Ile Cys Lys Glu Ala Pro Arg
      180             185             190

Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Ala Lys Asn
      195             200             205

Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly Asn Gly Gly Cys Gln
      210             215             220

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Ser | Cys | Asp | Asp | Thr | Ala | Asp | Gly | Pro | Glu | Cys | Ser | Cys | His | Pro |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Gln | Tyr | Lys | Met | His | Thr | Asp | Gly | Arg | Ser | Cys | Leu | Glu | Arg | Glu | Asp |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Thr | Val | Leu | Glu | Val | Thr | Glu | Ser | Asn | Thr | Thr | Ser | Val | Val | Asp | Gly |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Asp | Lys | Arg | Val | Lys | Arg | Arg | Leu | Leu | Met | Glu | Thr | Cys | Ala | Val | Asn |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Asn | Gly | Gly | Cys | Asp | Arg | Thr | Cys | Lys | Asp | Thr | Ser | Thr | Gly | Val | His |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Cys | Ser | Cys | Pro | Val | Gly | Phe | Thr | Leu | Gln | Leu | Asp | Gly | Lys | Thr | Cys |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Lys | Asp | Ile | Asp | Glu | Cys | Gln | Thr | Arg | Asn | Gly | Gly | Cys | Asp | His | Phe |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Cys | Lys | Asn | Ile | Val | Gly | Ser | Phe | Asp | Cys | Gly | Cys | Lys | Lys | Gly | Phe |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Lys | Leu | Leu | Thr | Asp | Glu | Lys | Ser | Cys | Gln | Asp | Val | Asp | Glu | Cys | Ser |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Leu | Asp | Arg | Thr | Cys | Asp | His | Ser | Cys | Ile | Asn | His | Pro | Gly | Thr | Phe |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Ala | Cys | Ala | Cys | Asn | Arg | Gly | Tyr | Thr | Leu | Tyr | Gly | Phe | Thr | His | Cys |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Gly | Asp | Val | Thr | Thr | Ile | Arg | Thr | Ser | Val | Thr | Phe | Lys | Leu | Asn | Glu |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Gly | Lys | Cys | Ser | Leu | Lys | Asn | Ala | Glu | Leu | Phe | Pro | Glu | Gly | Leu | Arg |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Pro | Ala | Leu | Pro | Glu | Lys | His | Ser | Ser | Val | Lys | Glu | Ser | Phe | Arg | Tyr |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Val | Asn | Leu | Thr | Cys | Ser | Ser | Gly | Lys | Gln | Val | Pro | Gly | Ala | Pro | Gly |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Arg | Pro | Ser | Thr | Pro | Lys | Glu | Met | Phe | Ile | Thr | Val | Glu | Phe | Glu | Leu |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Glu | Thr | Asn | Gln | Lys | Glu | Val | Thr | Ala | Ser | Cys | Asp | Leu | Ser | Cys | Ile |
|     |     |     |     | 485 |     |     |     | 490 |     |     |     |     |     | 495 |     |
| Val | Lys | Arg | Thr | Glu | Lys | Arg | Leu | Arg | Lys | Ala | Ile | Arg | Thr | Leu | Arg |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Lys | Ala | Val | His | Arg | Glu | Gln | Phe | His | Leu | Gln | Leu | Ser | Gly | Met | Asn |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Leu | Asp | Val | Ala | Lys | Lys | Pro | Pro | Arg | Thr | Ser | Glu | Arg | Gln | Ala | Glu |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
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| Arg | Ala | Gly | Thr | Tyr | Thr | Asp | Gly | Ala | Arg | Glu | Arg | Cys | Ile | Leu | Cys |
|     |     |     |     | 565 |     |     |     | 570 |     |     |     |     |     | 575 |     |
| Pro | Asn | Gly | Thr | Phe | Gln | Asn | Glu | Glu | Gly | Gln | Met | Thr | Cys | Glu | Pro |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Cys | Pro | Arg | Pro | Gly | Asn | Ser | Gly | Ala | Leu | Lys | Thr | Pro | Glu | Ala | Trp |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Asn | Met | Ser | Glu | Cys | Gly | Gly | Leu | Cys | Gln | Pro | Gly | Glu | Tyr | Ser | Ala |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |

-continued

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Asp Gly Phe Ala Pro Cys Gln Leu Cys Ala Leu Gly Thr Phe Gln Pro  
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 Glu Ala Gly Arg Thr Ser Cys Phe Pro Cys Gly Gly Gly Leu Ala Thr  
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 Lys His Gln Gly Ala Thr Ser Phe Gln Asp Cys Glu Thr Arg Val Gln  
 660 665 670  
 Cys Ser Pro Gly His Phe Tyr Asn Thr Thr Thr His Arg Cys Ile Arg  
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 Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe Gly Lys Asn Asn Cys Val  
 690 695 700  
 Ser Cys Pro Gly Asn Thr Thr Thr Asp Phe Asp Gly Ser Thr Asn Ile  
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 Thr Gln Cys Lys Asn Arg Arg Cys Gly Gly Glu Leu Gly Asp Phe Thr  
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 Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala Asn Thr  
 740 745 750  
 Glu Cys Thr Trp Thr Ile Asn Pro Pro Pro Lys Arg Arg Ile Leu Ile  
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 Val Val Pro Glu Ile Phe Leu Pro Ile Glu Asp Asp Cys Gly Asp Tyr  
 770 775 780  
 Leu Val Met Arg Lys Thr Ser Ser Ser Asn Ser Val Thr Thr Tyr Glu  
 785 790 795 800  
 Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala Phe Thr Ser Arg Ser Lys  
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 Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu Gly Asn Ser Ala Arg Gly  
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 Phe Gln Val Pro Tyr Val Thr Tyr Asp Glu Asp Tyr Gln Glu Leu Ile  
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 Glu Asp Ile Val Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His Gln  
 850 855 860  
 Glu Ile Leu Lys Asp Lys Lys Leu Ile Lys Ala Leu Phe Asp Val Leu  
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 Ala His Pro Gln Asn Tyr Phe Lys Tyr Thr Ala Gln Glu Ser Arg Glu  
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 gcc tgg gcg gtg ctg ctg ctg ctg ctg cta cca ctg ctg ctg ctg 161  
 Ala Trp Ala Val Leu Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Leu

| 15  |     |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     |     |      |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|
| gtg | ggg | gcc | gtc | cgc | ccg | ggg | cgg | ggc | cgt | gcc | gcg | ggg | ccg | cag | gag | 209  |  |
| Val | Gly | Ala | Val | Pro | Pro | Gly | Arg | Gly | Arg | Ala | Ala | Gly | Pro | Gln | Glu |      |  |
| 30  |     |     |     |     | 35  |     |     |     |     | 40  |     |     |     |     |     |      |  |
| gat | gta | gat | gag | tgt | gcc | caa | ggg | cta | gat | gac | tgc | cat | gcc | gac | gcc | 257  |  |
| Asp | Val | Asp | Glu | Cys | Ala | Gln | Gly | Leu | Asp | Asp | Cys | His | Ala | Asp | Ala |      |  |
| 45  |     |     |     |     | 50  |     |     |     |     | 55  |     |     |     |     |     |      |  |
| ctg | tgt | cag | aac | aca | ccc | acc | tcc | tac | aag | tgc | tcc | tgc | aag | cct | ggc | 305  |  |
| Leu | Cys | Gln | Asn | Thr | Pro | Thr | Ser | Tyr | Lys | Cys | Ser | Cys | Lys | Pro | Gly |      |  |
| 60  |     |     |     |     | 65  |     |     |     |     | 70  |     |     |     |     | 75  |      |  |
| tac | caa | ggg | gaa | ggc | agg | cag | tgt | gag | gac | atc | gat | gaa | tgt | gga | aat | 353  |  |
| Tyr | Gln | Gly | Glu | Gly | Arg | Gln | Cys | Glu | Asp | Ile | Asp | Glu | Cys | Gly | Asn |      |  |
| 80  |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     |     |      |  |
| gag | ctc | aat | gga | ggc | tgt | gtc | cat | gac | tgt | ttg | aat | att | cca | ggc | aat | 401  |  |
| Glu | Leu | Asn | Gly | Gly | Cys | Val | His | Asp | Cys | Leu | Asn | Ile | Pro | Gly | Asn |      |  |
| 95  |     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     |      |  |
| tat | cgt | tgc | act | tgt | ttt | gat | ggc | ttc | atg | ttg | gct | cat | gac | ggg | cat | 449  |  |
| Tyr | Arg | Cys | Thr | Cys | Phe | Asp | Gly | Phe | Met | Leu | Ala | His | Asp | Gly | His |      |  |
| 110 |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     |     |      |  |
| aat | tgt | ctt | gat | gtg | gac | gag | tgc | ctg | gag | aac | aat | ggc | ggc | tgc | cag | 497  |  |
| Asn | Cys | Leu | Asp | Val | Asp | Glu | Cys | Leu | Glu | Asn | Asn | Gly | Gly | Cys | Gln |      |  |
| 125 |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |     |      |  |
| cat | acc | tgt | gtc | aac | gtc | atg | ggg | agc | tat | gag | tgc | tgc | tgc | aag | gag | 545  |  |
| His | Thr | Cys | Val | Asn | Val | Met | Gly | Ser | Tyr | Glu | Cys | Cys | Cys | Lys | Glu |      |  |
| 140 |     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |      |  |
| ggg | ttt | ttc | ctg | agt | gac | aat | cag | cac | acc | tgc | att | cac | cgc | tcg | gaa | 593  |  |
| Gly | Phe | Phe | Leu | Ser | Asp | Asn | Gln | His | Thr | Cys | Ile | His | Arg | Ser | Glu |      |  |
| 160 |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     |      |  |
| gag | ggc | ctg | agc | tgc | atg | aat | aag | gat | cac | ggc | tgt | agt | cac | atc | tgc | 641  |  |
| Glu | Gly | Leu | Ser | Cys | Met | Asn | Lys | Asp | His | Gly | Cys | Ser | His | Ile | Cys |      |  |
| 175 |     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |     |      |  |
| aag | gag | gcc | cca | agg | ggc | agc | gtc | gcc | tgt | gag | tgc | agg | cct | ggg | ttt | 689  |  |
| Lys | Glu | Ala | Pro | Arg | Gly | Ser | Val | Ala | Cys | Glu | Cys | Arg | Pro | Gly | Phe |      |  |
| 190 |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     |     |      |  |
| gag | ctg | gcc | aag | aac | cag | aga | gac | tgc | atc | ttg | acc | tgt | aac | cat | ggg | 737  |  |
| Glu | Leu | Ala | Lys | Asn | Gln | Arg | Asp | Cys | Ile | Leu | Thr | Cys | Asn | His | Gly |      |  |
| 205 |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     |     |      |  |
| aac | ggg | ggg | tgc | cag | cac | tcc | tgt | gac | gat | aca | gcc | gat | ggc | cca | gag | 785  |  |
| Asn | Gly | Gly | Cys | Gln | His | Ser | Cys | Asp | Asp | Thr | Ala | Asp | Gly | Pro | Glu |      |  |
| 220 |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |      |  |
| tgc | agc | tgc | cat | cca | cag | tac | aag | atg | cac | aca | gat | ggg | agg | agc | tgc | 833  |  |
| Cys | Ser | Cys | His | Pro | Gln | Tyr | Lys | Met | His | Thr | Asp | Gly | Arg | Ser | Cys |      |  |
| 240 |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     |     |      |  |
| ctt | gag | cga | gag | gac | act | gtc | ctg | gag | gtg | aca | gag | agc | aac | acc | aca | 881  |  |
| Leu | Glu | Arg | Glu | Asp | Thr | Val | Leu | Glu | Val | Thr | Glu | Ser | Asn | Thr | Thr |      |  |
| 255 |     |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     |     |      |  |
| tca | gtg | gtg | gat | ggg | gat | aaa | cgg | gtg | aaa | cgg | cgg | ctg | ctc | atg | gaa | 929  |  |
| Ser | Val | Val | Asp | Gly | Asp | Lys | Arg | Val | Lys | Arg | Arg | Leu | Leu | Met | Glu |      |  |
| 270 |     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |     |     |      |  |
| acg | tgt | gct | gtc | aac | aat | gga | ggc | tgt | gac | cgc | acc | tgt | aag | gat | act | 977  |  |
| Thr | Cys | Ala | Val | Asn | Asn | Gly | Gly | Cys | Asp | Arg | Thr | Cys | Lys | Asp | Thr |      |  |
| 285 |     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     |     |      |  |
| tcg | aca | ggg | gtc | cac | tgc | agt | tgt | cct | gtt | gga | ttc | act | ctc | cag | ttg | 1025 |  |
| Ser | Thr | Gly | Val | His | Cys | Ser | Cys | Pro | Val | Gly | Phe | Thr | Leu | Gln | Leu |      |  |
| 300 |     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |      |  |
| gat | ggg | aag | aca | tgt | aaa | gat | att | gat | gag | tgc | cag | acc | cgc | aat | gga | 1073 |  |
| Asp | Gly | Lys | Thr | Cys | Lys | Asp | Ile | Asp | Glu | Cys | Gln | Thr | Arg | Asn | Gly |      |  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|------|--|--|-----|--|--|--|--|--|--|--|--|--|--|
| 320 |     |     |     |     |     |     |     |     |     | 325 |     |     |     |     |     |  |      |  |  | 330 |  |  |  |  |  |  |  |  |  |  |
| ggt | tgt | gat | cat | ttc | tgc | aaa | aac | atc | gtg | ggc | agt | ttt | gac | tgc | ggc |  | 1121 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Gly | Cys | Asp | His | Phe | Cys | Lys | Asn | Ile | Val | Gly | Ser | Phe | Asp | Cys | Gly |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 335 |     |     |     | 340 |     |     |     | 345 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| tgc | aag | aaa | gga | ttt | aaa | tta | tta | aca | gat | gag | aag | tct | tgc | caa | gat |  | 1169 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Cys | Lys | Lys | Gly | Phe | Lys | Leu | Leu | Thr | Asp | Glu | Lys | Ser | Cys | Gln | Asp |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 350 |     |     |     | 355 |     |     |     | 360 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| gtg | gat | gag | tgc | tct | ttg | gat | agg | acc | tgt | gac | cac | agc | tgc | atc | aac |  | 1217 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Val | Asp | Glu | Cys | Ser | Leu | Asp | Arg | Thr | Cys | Asp | His | Ser | Cys | Ile | Asn |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 365 |     |     |     | 370 |     |     |     | 375 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| cac | cct | ggc | aca | ttt | gct | tgt | gct | tgc | aac | cga | ggg | tac | acc | ctg | tat |  | 1265 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| His | Pro | Gly | Thr | Phe | Ala | Cys | Ala | Cys | Asn | Arg | Gly | Tyr | Thr | Leu | Tyr |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 380 |     |     |     | 385 |     |     |     | 390 |     |     |     | 395 |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| ggc | ttc | acc | cac | tgt | gga | gac | acc | aat | gag | tgc | agc | atc | aac | aac | gga |  | 1313 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Gly | Phe | Thr | His | Cys | Gly | Asp | Thr | Asn | Glu | Cys | Ser | Ile | Asn | Asn | Gly |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 400 |     |     |     | 405 |     |     |     | 410 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
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| Gly | Cys | Gln | Gln | Val | Cys | Val | Asn | Thr | Val | Gly | Ser | Tyr | Glu | Cys | Gln |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 415 |     |     |     | 420 |     |     |     | 425 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| tgc | cac | cct | ggg | tac | aag | ctc | cac | tgg | aat | aaa | aaa | gac | tgt | gtg | gct |  | 1409 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Cys | His | Pro | Gly | Tyr | Lys | Leu | His | Trp | Asn | Lys | Lys | Asp | Cys | Val | Ala |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 430 |     |     |     | 435 |     |     |     | 440 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
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| Ser | Cys | Asp | Leu | Ser | Cys | Ile | Val | Lys | Arg | Thr | Glu | Lys | Arg | Leu | Arg |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 445 |     |     |     | 450 |     |     |     | 455 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
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| Lys | Ala | Ile | Arg | Thr | Leu | Arg | Lys | Ala | Val | His | Arg | Glu | Gln | Phe | His |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 460 |     |     |     | 465 |     |     |     | 470 |     |     |     | 475 |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| ctc | cag | ctc | tca | ggc | atg | aac | ctc | gac | gtg | gct | aaa | aag | cct | ccc | aga |  | 1553 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Leu | Gln | Leu | Ser | Gly | Met | Asn | Leu | Asp | Val | Ala | Lys | Lys | Pro | Pro | Arg |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 480 |     |     |     | 485 |     |     |     | 490 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| aca | tct | gaa | cgc | cag | gca | gag | tcc | tgt | gga | gtg | ggc | cag | ggg | cat | gca |  | 1601 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Thr | Ser | Glu | Arg | Gln | Ala | Glu | Ser | Cys | Gly | Val | Gly | Gln | Gly | His | Ala |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 495 |     |     |     | 500 |     |     |     | 505 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| gaa | aac | caa | tgt | gtc | agt | tgc | agg | gct | ggg | acc | tat | tat | gat | gga | gca |  | 1649 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Glu | Asn | Gln | Cys | Val | Ser | Cys | Arg | Ala | Gly | Thr | Tyr | Tyr | Asp | Gly | Ala |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 510 |     |     |     | 515 |     |     |     | 520 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| cga | gaa | cgc | tgc | att | tta | tgt | cca | aat | gga | acc | ttc | caa | aat | gag | gaa |  | 1697 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Arg | Glu | Arg | Cys | Ile | Leu | Cys | Pro | Asn | Gly | Thr | Phe | Gln | Asn | Glu | Glu |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 525 |     |     |     | 530 |     |     |     | 535 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| gga | caa | atg | act | tgt | gaa | cca | tgc | cca | aga | cca | gga | aat | tct | ggg | gcc |  | 1745 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Gly | Gln | Met | Thr | Cys | Glu | Pro | Cys | Pro | Arg | Pro | Gly | Asn | Ser | Gly | Ala |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 540 |     |     |     | 545 |     |     |     | 550 |     |     |     | 555 |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| ctg | aag | acc | cca | gaa | gct | tgg | aat | atg | tct | gaa | tgt | gga | ggg | ctg | tgt |  | 1793 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Leu | Lys | Thr | Pro | Glu | Ala | Trp | Asn | Met | Ser | Glu | Cys | Gly | Gly | Leu | Cys |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 560 |     |     |     | 565 |     |     |     | 570 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| caa | cct | ggg | gaa | tat | tct | gca | gat | ggc | ttt | gca | cct | tgc | cag | ctc | tgt |  | 1841 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Gln | Pro | Gly | Glu | Tyr | Ser | Ala | Asp | Gly | Phe | Ala | Pro | Cys | Gln | Leu | Cys |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 575 |     |     |     | 580 |     |     |     | 585 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| gcc | ctg | ggc | acg | ttc | cag | cct | gaa | gct | ggg | cga | act | tcc | tgc | ttc | ccc |  | 1889 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Ala | Leu | Gly | Thr | Phe | Gln | Pro | Glu | Ala | Gly | Arg | Thr | Ser | Cys | Phe | Pro |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 590 |     |     |     | 595 |     |     |     | 600 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| tgt | gga | gga | ggc | ctt | gcc | acc | aaa | cat | cag | gga | gct | act | tcc | ttt | cag |  | 1937 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Cys | Gly | Gly | Gly | Leu | Ala | Thr | Lys | His | Gln | Gly | Ala | Thr | Ser | Phe | Gln |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| 605 |     |     |     | 610 |     |     |     | 615 |     |     |     |     |     |     |     |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |
| gac | tgt | gaa | acc | aga | gtt | caa | tgt | tca | cct | gga | cat | ttc | tac | aac | acc |  | 1985 |  |  |     |  |  |  |  |  |  |  |  |  |  |
| Asp | Cys | Glu | Thr | Arg | Val | Gln | Cys | Ser | Pro | Gly | His | Phe | Tyr | Asn | Thr |  |      |  |  |     |  |  |  |  |  |  |  |  |  |  |

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| 620                                                                | 625 | 630 | 635 |      |
|--------------------------------------------------------------------|-----|-----|-----|------|
| acc act cac cga tgt att cgt tgc cca gtg gga aca tac cag cct gaa    |     |     |     | 2033 |
| Thr Thr His Arg Cys Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu    |     |     |     |      |
|                                                                    | 640 | 645 | 650 |      |
| ttt gga aaa aat aat tgt gtt tct tgc cca gga aat act acg act gac    |     |     |     | 2081 |
| Phe Gly Lys Asn Asn Cys Val Ser Cys Pro Gly Asn Thr Thr Thr Asp    |     |     |     |      |
|                                                                    | 655 | 660 | 665 |      |
| ttt gat ggc tcc aca aac ata acc cag tgt aaa aac aga aga tgt gga    |     |     |     | 2129 |
| Phe Asp Gly Ser Thr Asn Ile Thr Gln Cys Lys Asn Arg Arg Cys Gly    |     |     |     |      |
|                                                                    | 670 | 675 | 680 |      |
| ggg gag ctg gga gat ttc act ggg tac att gaa tcc cca aac tac cca    |     |     |     | 2177 |
| Gly Glu Leu Gly Asp Phe Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro    |     |     |     |      |
|                                                                    | 685 | 690 | 695 |      |
| ggc aat tac cca gcc aac acc gag tgt acg tgg acc atc aac cca ccc    |     |     |     | 2225 |
| Gly Asn Tyr Pro Ala Asn Thr Glu Cys Thr Trp Thr Ile Asn Pro Pro    |     |     |     |      |
|                                                                    | 700 | 705 | 710 | 715  |
| ccc aag cgc cgc atc ctg atc gtg gtc cct gag atc ttc ctg ccc ata    |     |     |     | 2273 |
| Pro Lys Arg Arg Ile Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile    |     |     |     |      |
|                                                                    | 720 | 725 | 730 |      |
| gag gac gac tgt ggg gac tat ctg gtg atg cgg aaa acc tct tca tcc    |     |     |     | 2321 |
| Glu Asp Asp Cys Gly Asp Tyr Leu Val Met Arg Lys Thr Ser Ser Ser    |     |     |     |      |
|                                                                    | 735 | 740 | 745 |      |
| aat tct gtg aca aca tat gaa acc tgc cag acc tac gaa cgc ccc atc    |     |     |     | 2369 |
| Asn Ser Val Thr Thr Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile    |     |     |     |      |
|                                                                    | 750 | 755 | 760 |      |
| gcc ttc acc tcc agg tca aag aag ctg tgg att cag ttc aag tcc aat    |     |     |     | 2417 |
| Ala Phe Thr Ser Arg Ser Lys Lys Leu Trp Ile Gln Phe Lys Ser Asn    |     |     |     |      |
|                                                                    | 765 | 770 | 775 |      |
| gaa ggg aac agc gct aga ggg ttc cag gtc cca tac gtg aca tat gat    |     |     |     | 2465 |
| Glu Gly Asn Ser Ala Arg Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp    |     |     |     |      |
|                                                                    | 780 | 785 | 790 | 795  |
| gag gac tac cag gaa ctc att gaa gac ata gtt cga gat ggc agg ctc    |     |     |     | 2513 |
| Glu Asp Tyr Gln Glu Leu Ile Glu Asp Ile Val Arg Asp Gly Arg Leu    |     |     |     |      |
|                                                                    | 800 | 805 | 810 |      |
| tat gca tct gag aac cat cag gaa ata ctt aag gat aag aaa ctt atc    |     |     |     | 2561 |
| Tyr Ala Ser Glu Asn His Gln Glu Ile Leu Lys Asp Lys Lys Leu Ile    |     |     |     |      |
|                                                                    | 815 | 820 | 825 |      |
| aag gct ctg ttt gat gtc ctg gcc cat ccc cag aac tat ttc aag tac    |     |     |     | 2609 |
| Lys Ala Leu Phe Asp Val Leu Ala His Pro Gln Asn Tyr Phe Lys Tyr    |     |     |     |      |
|                                                                    | 830 | 835 | 840 |      |
| aca gcc cag gag tcc cga gag atg ttt cca aga tgc ttc atc cga ttg    |     |     |     | 2657 |
| Thr Ala Gln Glu Ser Arg Glu Met Phe Pro Arg Ser Phe Ile Arg Leu    |     |     |     |      |
|                                                                    | 845 | 850 | 855 |      |
| cta cgt tcc aaa gtg tcc agg ttt ttg aga cct tac aaa tga            |     |     |     | 2699 |
| Leu Arg Ser Lys Val Ser Arg Phe Leu Arg Pro Tyr Lys *              |     |     |     |      |
|                                                                    | 860 | 865 | 870 |      |
| ctcagccac gtgccactca atacaaatgt tctgctatag gggttggtggg acagagctgt  |     |     |     | 2759 |
| cttcttctct catgtcagca cagtcgggta ttgctgcctc ccgtatcagt gactcattag  |     |     |     | 2819 |
| agttcaattt ttatagataa tacagatatt ttggtaaatt gaacttggtt tttctttccc  |     |     |     | 2879 |
| agcatcgtgg atgtagactg agaatggctt tgagtggcat cagcttctca ctgctgtggg  |     |     |     | 2939 |
| cggatgtctt ggatagatca cgggctggct gagctggact ttggtcagcc taggtgagac  |     |     |     | 2999 |
| tcaactgtcc tttctggggtc ttactcctcc tcaaggagtc tgtagtggaa aggaggccac |     |     |     | 3059 |
| agaataagct gcttattctg aaacttcagc ttcctctagc ccggccctct ctaaggggagc |     |     |     | 3119 |

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cctctgcact cgtgtgcagg ctctgaccag gcagaacagg caagagggga gggaaggaga 3179
ccctcgcagg ctccctccac ccaccttgag acctgggagg actcagtttc tccacagcct 3239
tctccagcct gtgtgataca agtttgatcc caggaacttg agttctaagc agtgctcgtg 3299
aaaaaaaaa gcagaaagaa ttagaataa ataaaaacta agcacttctg gagacat 3356

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<210> SEQ ID NO 58
<211> LENGTH: 872
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 58

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Met Gly Val Ala Gly Arg Asn Arg Pro Gly Ala Ala Trp Ala Val Leu
1      5      10      15
Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Val Gly Ala Val Pro
20     25     30
Pro Gly Arg Gly Arg Ala Ala Gly Pro Gln Glu Asp Val Asp Glu Cys
35     40     45
Ala Gln Gly Leu Asp Asp Cys His Ala Asp Ala Leu Cys Gln Asn Thr
50     55     60
Pro Thr Ser Tyr Lys Cys Ser Cys Lys Pro Gly Tyr Gln Gly Glu Gly
65     70     75     80
Arg Gln Cys Glu Asp Ile Asp Glu Cys Gly Asn Glu Leu Asn Gly Gly
85     90     95
Cys Val His Asp Cys Leu Asn Ile Pro Gly Asn Tyr Arg Cys Thr Cys
100    105    110
Phe Asp Gly Phe Met Leu Ala His Asp Gly His Asn Cys Leu Asp Val
115    120    125
Asp Glu Cys Leu Glu Asn Asn Gly Gly Cys Gln His Thr Cys Val Asn
130    135    140
Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu Gly Phe Phe Leu Ser
145    150    155    160
Asp Asn Gln His Thr Cys Ile His Arg Ser Glu Glu Gly Leu Ser Cys
165    170    175
Met Asn Lys Asp His Gly Cys Ser His Ile Cys Lys Glu Ala Pro Arg
180    185    190
Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Ala Lys Asn
195    200    205
Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly Asn Gly Gly Cys Gln
210    215    220
His Ser Cys Asp Asp Thr Ala Asp Gly Pro Glu Cys Ser Cys His Pro
225    230    235    240
Gln Tyr Lys Met His Thr Asp Gly Arg Ser Cys Leu Glu Arg Glu Asp
245    250    255
Thr Val Leu Glu Val Thr Glu Ser Asn Thr Thr Ser Val Val Asp Gly
260    265    270
Asp Lys Arg Val Lys Arg Arg Leu Leu Met Glu Thr Cys Ala Val Asn
275    280    285
Asn Gly Gly Cys Asp Arg Thr Cys Lys Asp Thr Ser Thr Gly Val His
290    295    300
Cys Ser Cys Pro Val Gly Phe Thr Leu Gln Leu Asp Gly Lys Thr Cys
305    310    315    320

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Asp | Ile | Asp | Glu | Cys | Gln | Thr | Arg | Asn | Gly | Gly | Cys | Asp | His | Phe |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     |     |     |
| Cys | Lys | Asn | Ile | Val | Gly | Ser | Phe | Asp | Cys | Gly | Cys | Lys | Lys | Gly | Phe |
|     |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     |     |     |
| Lys | Leu | Leu | Thr | Asp | Glu | Lys | Ser | Cys | Gln | Asp | Val | Asp | Glu | Cys | Ser |
|     |     |     |     | 355 |     |     |     |     | 360 |     |     |     |     |     |     |
| Leu | Asp | Arg | Thr | Cys | Asp | His | Ser | Cys | Ile | Asn | His | Pro | Gly | Thr | Phe |
|     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     |     |     |
| Ala | Cys | Ala | Cys | Asn | Arg | Gly | Tyr | Thr | Leu | Tyr | Gly | Phe | Thr | His | Cys |
|     |     |     |     | 385 |     |     |     |     | 390 |     |     |     |     |     |     |
| Gly | Asp | Thr | Asn | Glu | Cys | Ser | Ile | Asn | Asn | Gly | Gly | Cys | Gln | Gln | Val |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     |     |     |
| Cys | Val | Asn | Thr | Val | Gly | Ser | Tyr | Glu | Cys | Gln | Cys | His | Pro | Gly | Tyr |
|     |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     |     |     |
| Lys | Leu | His | Trp | Asn | Lys | Lys | Asp | Cys | Val | Ala | Ser | Cys | Asp | Leu | Ser |
|     |     |     |     | 435 |     |     |     |     | 440 |     |     |     |     |     |     |
| Cys | Ile | Val | Lys | Arg | Thr | Glu | Lys | Arg | Leu | Arg | Lys | Ala | Ile | Arg | Thr |
|     |     |     |     | 450 |     |     |     |     | 455 |     |     |     |     |     |     |
| Leu | Arg | Lys | Ala | Val | His | Arg | Glu | Gln | Phe | His | Leu | Gln | Leu | Ser | Gly |
|     |     |     |     | 465 |     |     |     |     | 470 |     |     |     |     |     |     |
| Met | Asn | Leu | Asp | Val | Ala | Lys | Lys | Pro | Pro | Arg | Thr | Ser | Glu | Arg | Gln |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |     |     |
| Ala | Glu | Ser | Cys | Gly | Val | Gly | Gln | Gly | His | Ala | Glu | Asn | Gln | Cys | Val |
|     |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     |     |     |
| Ser | Cys | Arg | Ala | Gly | Thr | Tyr | Tyr | Asp | Gly | Ala | Arg | Glu | Arg | Cys | Ile |
|     |     |     |     | 515 |     |     |     |     | 520 |     |     |     |     |     |     |
| Leu | Cys | Pro | Asn | Gly | Thr | Phe | Gln | Asn | Glu | Glu | Gly | Gln | Met | Thr | Cys |
|     |     |     |     | 530 |     |     |     |     | 535 |     |     |     |     |     |     |
| Glu | Pro | Cys | Pro | Arg | Pro | Gly | Asn | Ser | Gly | Ala | Leu | Lys | Thr | Pro | Glu |
|     |     |     |     | 545 |     |     |     |     | 550 |     |     |     |     |     |     |
| Ala | Trp | Asn | Met | Ser | Glu | Cys | Gly | Gly | Leu | Cys | Gln | Pro | Gly | Glu | Tyr |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     |     |     |
| Ser | Ala | Asp | Gly | Phe | Ala | Pro | Cys | Gln | Leu | Cys | Ala | Leu | Gly | Thr | Phe |
|     |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     |     |     |
| Gln | Pro | Glu | Ala | Gly | Arg | Thr | Ser | Cys | Phe | Pro | Cys | Gly | Gly | Gly | Leu |
|     |     |     |     | 595 |     |     |     |     | 600 |     |     |     |     |     |     |
| Ala | Thr | Lys | His | Gln | Gly | Ala | Thr | Ser | Phe | Gln | Asp | Cys | Glu | Thr | Arg |
|     |     |     |     | 610 |     |     |     |     | 615 |     |     |     |     |     |     |
| Val | Gln | Cys | Ser | Pro | Gly | His | Phe | Tyr | Asn | Thr | Thr | Thr | His | Arg | Cys |
|     |     |     |     | 625 |     |     |     |     | 630 |     |     |     |     |     |     |
| Ile | Arg | Cys | Pro | Val | Gly | Thr | Tyr | Gln | Pro | Glu | Phe | Gly | Lys | Asn | Asn |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     |     |     |
| Cys | Val | Ser | Cys | Pro | Gly | Asn | Thr | Thr | Thr | Asp | Phe | Asp | Gly | Ser | Thr |
|     |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     |     |     |
| Asn | Ile | Thr | Gln | Cys | Lys | Asn | Arg | Arg | Cys | Gly | Gly | Glu | Leu | Gly | Asp |
|     |     |     |     | 675 |     |     |     |     | 680 |     |     |     |     |     |     |
| Phe | Thr | Gly | Tyr | Ile | Glu | Ser | Pro | Asn | Tyr | Pro | Gly | Asn | Tyr | Pro | Ala |
|     |     |     |     | 690 |     |     |     |     | 695 |     |     |     |     |     |     |
| Asn | Thr | Glu | Cys | Thr | Trp | Thr | Ile | Asn | Pro | Pro | Pro | Lys | Arg | Arg | Ile |
|     |     |     |     | 705 |     |     |     |     | 710 |     |     |     |     |     |     |
| Leu | Ile | Val | Val | Pro | Glu | Ile | Phe | Leu | Pro | Ile | Glu | Asp | Asp | Cys | Glu |

[illegible]

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| 125                                                                                                                                                   | 130 | 135 |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| cat acc tgt gtc aac gtc atg ggg agc tat gag tgc tgc tgc aag gag<br>His Thr Cys Val Asn Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu<br>140 145 150 155 |     |     | 545  |
| ggg ttt ttc ctg agt gac aat cag cac acc tgc att cac cgc tcg gaa<br>Gly Phe Phe Leu Ser Asp Asn Gln His Thr Cys Ile His Arg Ser Glu<br>160 165 170     |     |     | 593  |
| gag ggc ctg agc tgc atg aat aag gat cac ggc tgt agt cac atc tgc<br>Glu Gly Leu Ser Cys Met Asn Lys Asp His Gly Cys Ser His Ile Cys<br>175 180 185     |     |     | 641  |
| aag gag gcc cca agg ggc agc gtc gcc tgt gag tgc agg cct ggt ttt<br>Lys Glu Ala Pro Arg Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe<br>190 195 200     |     |     | 689  |
| gag ctg gcc aag aac cag aga gac tgc atc ttg acc tgt aac cat ggg<br>Glu Leu Ala Lys Asn Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly<br>205 210 215     |     |     | 737  |
| aac ggt ggg tgc cag cac tcc tgt gac gat aca gcc gat ggc cca gag<br>Asn Gly Gly Cys Gln His Ser Cys Asp Asp Thr Ala Asp Gly Pro Glu<br>220 225 230 235 |     |     | 785  |
| tgc agc tgc cat cca cag tac aag atg cac aca gat ggg agg agc tgc<br>Cys Ser Cys His Pro Gln Tyr Lys Met His Thr Asp Gly Arg Ser Cys<br>240 245 250     |     |     | 833  |
| ctt gag cga gag gac act gtc ctg gag gtg aca gag agc aac acc aca<br>Leu Glu Arg Glu Asp Thr Val Leu Glu Val Thr Glu Ser Asn Thr Thr<br>255 260 265     |     |     | 881  |
| tca gtg gtg gat ggg gat aaa cgg gtg aaa cgg cgg ctg ctc atg gaa<br>Ser Val Val Asp Gly Asp Lys Arg Val Lys Arg Arg Leu Leu Met Glu<br>270 275 280     |     |     | 929  |
| acg tgt gct gtc aac aat gga ggc tgt gac cgc acc tgt aag gat act<br>Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Arg Thr Cys Lys Asp Thr<br>285 290 295     |     |     | 977  |
| tcg aca ggt gtc cac tgc agt tgt cct gtt gga ttc act ctc cag ttg<br>Ser Thr Gly Val His Cys Ser Cys Pro Val Gly Phe Thr Leu Gln Leu<br>300 305 310 315 |     |     | 1025 |
| gat ggg aag aca tgt aaa gat att gat gag tgc cag acc cgc aat gga<br>Asp Gly Lys Thr Cys Lys Asp Ile Asp Glu Cys Gln Thr Arg Asn Gly<br>320 325 330     |     |     | 1073 |
| ggt tgt gat cat ttc tgc aaa aac atc gtg ggc agt ttt gac tgc ggc<br>Gly Cys Asp His Phe Cys Lys Asn Ile Val Gly Ser Phe Asp Cys Gly<br>335 340 345     |     |     | 1121 |
| tgc aag aaa gga ttt aaa tta tta aca gat gag aag tct tgc caa gat<br>Cys Lys Lys Gly Phe Lys Leu Leu Thr Asp Glu Lys Ser Cys Gln Asp<br>350 355 360     |     |     | 1169 |
| gtg gat gag tgc tct ttg gat agg acc tgt gac cac agc tgc atc aac<br>Val Asp Glu Cys Ser Leu Asp Arg Thr Cys Asp His Ser Cys Ile Asn<br>365 370 375     |     |     | 1217 |
| cac cct ggc aca ttt gct tgt gct tgc aac cga ggg tac acc ctg tat<br>His Pro Gly Thr Phe Ala Cys Ala Cys Asn Arg Gly Tyr Thr Leu Tyr<br>380 385 390 395 |     |     | 1265 |
| ggc ttc acc cac tgt gga gac acc aat gag tgc agc atc aac aac gga<br>Gly Phe Thr His Cys Gly Asp Thr Asn Glu Cys Ser Ile Asn Asn Gly<br>400 405 410     |     |     | 1313 |
| ggc tgt cag cag gtc tgt gtg aac aca gtg ggc agc tat gaa tgc cag<br>Gly Cys Gln Val Cys Val Asn Thr Val Gly Ser Tyr Glu Cys Gln<br>415 420 425         |     |     | 1361 |
| tgc cac cct ggg tac aag ctc cac tgg aat aaa aaa gac tgt gtg gaa<br>Cys His Pro Gly Tyr Lys Leu His Trp Asn Lys Lys Asp Cys Val Glu<br>1409            |     |     |      |

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| 430                                                                                                                                                   | 435 | 440 |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| gtg aag ggg ctc ctg ccc aca agt gtg tca ccc cgt gtg tcc ctg cac<br>Val Lys Gly Leu Leu Pro Thr Ser Val Ser Pro Arg Val Ser Leu His<br>445 450 455     |     |     | 1457 |
| tgc ggt aag agt ggt gga gga gac ggg tgc ttc ctc aga tgt cac tct<br>Cys Gly Lys Ser Gly Gly Gly Asp Gly Cys Phe Leu Arg Cys His Ser<br>460 465 470 475 |     |     | 1505 |
| ggc att cac ctc tct tca gga ctg caa ggg gcc tac tct gtc acc tgt<br>Gly Ile His Leu Ser Ser Gly Leu Gln Gly Ala Tyr Ser Val Thr Cys<br>480 485 490     |     |     | 1553 |
| ggc tct tcc tct cct ctc agg aac aaa caa caa aaa tca aat gac tct<br>Gly Ser Ser Ser Pro Leu Arg Asn Lys Gln Gln Lys Ser Asn Asp Ser<br>495 500 505     |     |     | 1601 |
| gct ttt ggg gat gtc acc acc atc agg aca agt gta acc ttt aag cta<br>Ala Phe Gly Asp Val Thr Thr Ile Arg Thr Ser Val Thr Phe Lys Leu<br>510 515 520     |     |     | 1649 |
| aat gaa ggc aag tgt agt ttg aaa aat gct gag ctg ttt ccc gag ggt<br>Asn Glu Gly Lys Cys Ser Leu Lys Asn Ala Glu Leu Phe Pro Glu Gly<br>525 530 535     |     |     | 1697 |
| ctg cga cca gca cta cca gag aag cac agc tca gta aaa gag agc ttc<br>Leu Arg Pro Ala Leu Pro Glu Lys His Ser Ser Val Lys Glu Ser Phe<br>540 545 550 555 |     |     | 1745 |
| cgc tac gta aac ctt aca tgc agc tct ggc aag caa gtc cca gga gcc<br>Arg Tyr Val Asn Leu Thr Cys Ser Ser Gly Lys Gln Val Pro Gly Ala<br>560 565 570     |     |     | 1793 |
| cct ggc cga cca agc acc cct aag gaa atg ttt atc act gtt gag ttt<br>Pro Gly Arg Pro Ser Thr Pro Lys Glu Met Phe Ile Thr Val Glu Phe<br>575 580 585     |     |     | 1841 |
| gag ctt gaa act aac caa aag gag gtg aca gct tct tgt gac ctg agc<br>Glu Leu Glu Thr Asn Gln Lys Glu Val Thr Ala Ser Cys Asp Leu Ser<br>590 595 600     |     |     | 1889 |
| tgc atc gta aag cga acc gag aag cgg ctc cgt aaa gcc atc cgc acg<br>Cys Ile Val Lys Arg Thr Glu Lys Arg Leu Arg Lys Ala Ile Arg Thr<br>605 610 615     |     |     | 1937 |
| ctc aga aag gcc gtc cac agg gag cag ttt cac ctc cag ctc tca ggc<br>Leu Arg Lys Ala Val His Arg Glu Gln Phe His Leu Gln Leu Ser Gly<br>620 625 630 635 |     |     | 1985 |
| atg aac ctc gac gtg gct aaa aag cct ccc aga aca tct gaa cgc cag<br>Met Asn Leu Asp Val Ala Lys Lys Pro Pro Arg Thr Ser Glu Arg Gln<br>640 645 650     |     |     | 2033 |
| gca gag tcc tgt gga gtg ggc cag ggt cat gca gaa aac caa tgt gtc<br>Ala Glu Ser Cys Gly Val Gly Gln Gly His Ala Glu Asn Gln Cys Val<br>655 660 665     |     |     | 2081 |
| agt tgc agg gct ggg acc tat tat gat gga gca cga gaa cgc tgc att<br>Ser Cys Arg Ala Gly Thr Tyr Asp Gly Ala Arg Glu Arg Cys Ile<br>670 675 680         |     |     | 2129 |
| tta tgt cca aat gga acc ttc caa aat gag gaa gga caa atg act tgt<br>Leu Cys Pro Asn Gly Thr Phe Gln Asn Glu Glu Gly Gln Met Thr Cys<br>685 690 695     |     |     | 2177 |
| gaa cca tgc cca aga cca gga aat tct ggg gcc ctg aag acc cca gaa<br>Glu Pro Cys Pro Arg Pro Gly Asn Ser Gly Ala Leu Lys Thr Pro Glu<br>700 705 710 715 |     |     | 2225 |
| gct tgg aat atg tct gaa tgt gga ggt ctg tgt caa cct ggt gaa tat<br>Ala Trp Asn Met Ser Glu Cys Gly Gly Cys Gln Pro Gly Glu Tyr<br>720 725 730         |     |     | 2273 |
| tct gca gat ggc ttt gca cct tgc cag ctc tgt gcc ctg ggc acg ttc<br>Ser Ala Asp Gly Phe Ala Pro Cys Gln Leu Cys Ala Leu Gly Thr Phe                    |     |     | 2321 |

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| 735                                                                                                                                                   | 740 | 745 |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| cag cct gaa gct ggt cga act tcc tgc ttc ccc tgt gga gga ggc ctt<br>Gln Pro Glu Ala Gly Arg Thr Ser Cys Phe Pro Cys Gly Gly Gly Leu<br>750 755 760     |     |     | 2369 |
| gcc acc aaa cat cag gga gct act tcc ttt cag gac tgt gaa acc aga<br>Ala Thr Lys His Gln Gly Ala Thr Ser Phe Gln Asp Cys Glu Thr Arg<br>765 770 775     |     |     | 2417 |
| gtt caa tgt tca cct gga cat ttc tac aac acc acc act cac cga tgt<br>Val Gln Cys Ser Pro Gly His Phe Tyr Asn Thr Thr Thr His Arg Cys<br>780 785 790 795 |     |     | 2465 |
| att cgt tgc cca gtg gga aca tac cag cct gaa ttt gga aaa aat aat<br>Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe Gly Lys Asn Asn<br>800 805 810     |     |     | 2513 |
| tgt gtt tct tgc cca gga aat act acg act gac ttt gat ggc tcc aca<br>Cys Val Ser Cys Pro Gly Asn Thr Thr Thr Asp Phe Asp Gly Ser Thr<br>815 820 825     |     |     | 2561 |
| aac ata acc cag tgt aaa aac aga aga tgt gga ggg gag ctg gga gat<br>Asn Ile Thr Gln Cys Lys Asn Arg Arg Cys Gly Gly Glu Leu Gly Asp<br>830 835 840     |     |     | 2609 |
| ttc act ggg tac att gaa tcc cca aac tac cca ggc aat tac cca gcc<br>Phe Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala<br>845 850 855     |     |     | 2657 |
| aac acc gag tgt acg tgg acc atc aac cca ccc ccc aag cgc cgc atc<br>Asn Thr Glu Cys Thr Trp Thr Ile Asn Pro Pro Pro Lys Arg Arg Ile<br>860 865 870 875 |     |     | 2705 |
| ctg atc gtg gtc cct gag atc ttc ctg ccc ata gag gac gac tgt ggg<br>Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu Asp Asp Cys Gly<br>880 885 890     |     |     | 2753 |
| gac tat ctg gtg atg cgg aaa acc tct tca tcc aat tct gtg aca aca<br>Asp Tyr Leu Val Met Arg Lys Thr Ser Ser Ser Asn Ser Val Thr Thr<br>895 900 905     |     |     | 2801 |
| tat gaa acc tgc cag acc tac gaa cgc ccc atc gcc ttc acc tcc agg<br>Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala Phe Thr Ser Arg<br>910 915 920     |     |     | 2849 |
| tca aag aag ctg tgg att cag ttc aag tcc aat gaa ggg aac agc gct<br>Ser Lys Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu Gly Asn Ser Ala<br>925 930 935     |     |     | 2897 |
| aga ggg ttc cag gtc cca tac gtg aca tat gat gag gac tac cag gaa<br>Arg Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Glu Asp Tyr Gln Glu<br>940 945 950 955 |     |     | 2945 |
| ctc att gaa gac ata gtt cga gat ggc agg ctc tat gca tct gag aac<br>Leu Ile Glu Asp Ile Val Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn<br>960 965 970     |     |     | 2993 |
| cat cag gaa ata ctt aag gat aag aaa ctt atc aag gct ctg ttt gat<br>His Gln Glu Ile Leu Lys Asp Lys Lys Leu Ile Lys Ala Leu Phe Asp<br>975 980 985     |     |     | 3041 |
| gtc ctg gcc cat ccc cag aac tat ttc aag tac aca gcc cag gag tcc<br>Val Leu Ala His Pro Gln Asn Tyr Phe Lys Tyr Thr Ala Gln Glu Ser<br>990 995 1000    |     |     | 3089 |
| cga gag atg ttt cca aga tgc ttc atc cga ttg cta cgt tcc aaa gtg<br>Arg Glu Met Phe Pro Arg Ser Phe Ile Arg Leu Leu Arg Ser Lys Val<br>1005 1010 1015  |     |     | 3137 |
| tcc agg ttt ttg aga cct tac aaa tga ctccagccac gtgccactca<br>Ser Arg Phe Leu Arg Pro Tyr Lys *                                                        |     |     | 3184 |
| 1020 1025                                                                                                                                             |     |     |      |
| atacaaatgt tctgctatag gggtgggtggg acagagctgt cttccttctg catgtcagca                                                                                    |     |     | 3244 |

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cagtcgggta ttgctgcctc ccgtatcagt gactcattag agttcaattt ttatagataa 3304
tacagatatt ttggtaaatt gaacttggtt tttctttccc agcatcgtgg atgtagactg 3364
agaatggcct tgagtggcat cagcttctca ctgctgtggg cggatgtcct ggatagatca 3424
cgggctggct gagctggact ttggtcagcc taggtgagac tcacctgtcc ttctggggtc 3484
ttactcctcc tcaaggagtc tgtagtgaa aggaggccac agaataagct gcttattctg 3544
aaacttcagc ttcctctagc cgggccctct ctaagggagc cctctgcact cgtgtgcagg 3604
ctctgaccag gcagaacagg caagagggga gggaaggaga cccctgcagg ctccctccac 3664
ccaccttgag acctgggagg actcagtttc tccacagcct tctccagcct gtgtgatata 3724
agtttgatcc caggaacttg agttctaagc agtgctcgtg aaaaaaaaaa gcagaaagaa 3784
ttagaaataa ataaaaacta agcacttctg gagacat 3821

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<210> SEQ ID NO 60
<211> LENGTH: 1027
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 60

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Met Gly Val Ala Gly Arg Asn Arg Pro Gly Ala Ala Trp Ala Val Leu
1      5      10      15
Leu Leu Leu Leu Leu Leu Pro Leu Leu Leu Val Gly Ala Val Pro
20     25     30
Pro Gly Arg Gly Arg Ala Ala Gly Pro Gln Glu Asp Val Asp Glu Cys
35     40     45
Ala Gln Gly Leu Asp Asp Cys His Ala Asp Ala Leu Cys Gln Asn Thr
50     55     60
Pro Thr Ser Tyr Lys Cys Ser Cys Lys Pro Gly Tyr Gln Gly Glu Gly
65     70     75     80
Arg Gln Cys Glu Asp Ile Asp Glu Cys Gly Asn Glu Leu Asn Gly Gly
85     90     95
Cys Val His Asp Cys Leu Asn Ile Pro Gly Asn Tyr Arg Cys Thr Cys
100    105    110
Phe Asp Gly Phe Met Leu Ala His Asp Gly His Asn Cys Leu Asp Val
115    120    125
Asp Glu Cys Leu Glu Asn Asn Gly Gly Cys Gln His Thr Cys Val Asn
130    135    140
Val Met Gly Ser Tyr Glu Cys Cys Cys Lys Glu Gly Phe Phe Leu Ser
145    150    155    160
Asp Asn Gln His Thr Cys Ile His Arg Ser Glu Glu Gly Leu Ser Cys
165    170    175
Met Asn Lys Asp His Gly Cys Ser His Ile Cys Lys Glu Ala Pro Arg
180    185    190
Gly Ser Val Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Ala Lys Asn
195    200    205
Gln Arg Asp Cys Ile Leu Thr Cys Asn His Gly Asn Gly Gly Cys Gln
210    215    220
His Ser Cys Asp Asp Thr Ala Asp Gly Pro Glu Cys Ser Cys His Pro
225    230    235    240
Gln Tyr Lys Met His Thr Asp Gly Arg Ser Cys Leu Glu Arg Glu Asp
245    250    255

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Leu | Glu | Val | Thr | Glu | Ser | Asn | Thr | Thr | Ser | Val | Val | Asp | Gly |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     |     | 270 |     |
| Asp | Lys | Arg | Val | Lys | Arg | Arg | Leu | Leu | Met | Glu | Thr | Cys | Ala | Val | Asn |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Asn | Gly | Gly | Cys | Asp | Arg | Thr | Cys | Lys | Asp | Thr | Ser | Thr | Gly | Val | His |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Cys | Ser | Cys | Pro | Val | Gly | Phe | Thr | Leu | Gln | Leu | Asp | Gly | Lys | Thr | Cys |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Lys | Asp | Ile | Asp | Glu | Cys | Gln | Thr | Arg | Asn | Gly | Gly | Cys | Asp | His | Phe |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Cys | Lys | Asn | Ile | Val | Gly | Ser | Phe | Asp | Cys | Gly | Cys | Lys | Lys | Gly | Phe |
|     |     | 340 |     |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Lys | Leu | Leu | Thr | Asp | Glu | Lys | Ser | Cys | Gln | Asp | Val | Asp | Glu | Cys | Ser |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Leu | Asp | Arg | Thr | Cys | Asp | His | Ser | Cys | Ile | Asn | His | Pro | Gly | Thr | Phe |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Ala | Cys | Ala | Cys | Asn | Arg | Gly | Tyr | Thr | Leu | Tyr | Gly | Phe | Thr | His | Cys |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Gly | Asp | Thr | Asn | Glu | Cys | Ser | Ile | Asn | Asn | Gly | Gly | Cys | Gln | Gln | Val |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Cys | Val | Asn | Thr | Val | Gly | Ser | Tyr | Glu | Cys | Gln | Cys | His | Pro | Gly | Tyr |
|     |     | 420 |     |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Lys | Leu | His | Trp | Asn | Lys | Lys | Asp | Cys | Val | Glu | Val | Lys | Gly | Leu | Leu |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Pro | Thr | Ser | Val | Ser | Pro | Arg | Val | Ser | Leu | His | Cys | Gly | Lys | Ser | Gly |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Gly | Gly | Asp | Gly | Cys | Phe | Leu | Arg | Cys | His | Ser | Gly | Ile | His | Leu | Ser |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Ser | Gly | Leu | Gln | Gly | Ala | Tyr | Ser | Val | Thr | Cys | Gly | Ser | Ser | Ser | Pro |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Leu | Arg | Asn | Lys | Gln | Gln | Lys | Ser | Asn | Asp | Ser | Ala | Phe | Gly | Asp | Val |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Thr | Thr | Ile | Arg | Thr | Ser | Val | Thr | Phe | Lys | Leu | Asn | Glu | Gly | Lys | Cys |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Ser | Leu | Lys | Asn | Ala | Glu | Leu | Phe | Pro | Glu | Gly | Leu | Arg | Pro | Ala | Leu |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Pro | Glu | Lys | His | Ser | Ser | Val | Lys | Glu | Ser | Phe | Arg | Tyr | Val | Asn | Leu |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Thr | Cys | Ser | Ser | Gly | Lys | Gln | Val | Pro | Gly | Ala | Pro | Gly | Arg | Pro | Ser |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Thr | Pro | Lys | Glu | Met | Phe | Ile | Thr | Val | Glu | Phe | Glu | Leu | Glu | Thr | Asn |
|     |     | 580 |     |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Gln | Lys | Glu | Val | Thr | Ala | Ser | Cys | Asp | Leu | Ser | Cys | Ile | Val | Lys | Arg |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Thr | Glu | Lys | Arg | Leu | Arg | Lys | Ala | Ile | Arg | Thr | Leu | Arg | Lys | Ala | Val |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| His | Arg | Glu | Gln | Phe | His | Leu | Gln | Leu | Ser | Gly | Met | Asn | Leu | Asp | Val |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Ala | Lys | Lys | Pro | Pro | Arg | Thr | Ser | Glu | Arg | Gln | Ala | Glu | Ser | Cys | Gly |
|     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     | 655 |     |
| Val | Gly | Gln | Gly | His | Ala | Glu | Asn | Gln | Cys | Val | Ser | Cys | Arg | Ala | Gly |

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| 660 |     |     |     |      | 665 |     |     |     |      | 670 |     |     |     |      |     |
|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|
| Thr | Tyr | Tyr | Asp | Gly  | Ala | Arg | Glu | Arg | Cys  | Ile | Leu | Cys | Pro | Asn  | Gly |
|     |     |     | 675 |      |     |     | 680 |     |      |     |     | 685 |     |      |     |
| Thr | Phe | Gln | Asn | Glu  | Glu | Gly | Gln | Met | Thr  | Cys | Glu | Pro | Cys | Pro  | Arg |
|     |     |     | 690 |      |     |     | 695 |     |      |     |     | 700 |     |      |     |
| Pro | Gly | Asn | Ser | Gly  | Ala | Leu | Lys | Thr | Pro  | Glu | Ala | Trp | Asn | Met  | Ser |
|     |     |     |     |      |     |     | 710 |     |      |     |     | 715 |     |      | 720 |
| Glu | Cys | Gly | Gly | Leu  | Cys | Gln | Pro | Gly | Glu  | Tyr | Ser | Ala | Asp | Gly  | Phe |
|     |     |     |     | 725  |     |     |     |     | 730  |     |     |     |     | 735  |     |
| Ala | Pro | Cys | Gln | Leu  | Cys | Ala | Leu | Gly | Thr  | Phe | Gln | Pro | Glu | Ala  | Gly |
|     |     |     |     | 740  |     |     |     |     | 745  |     |     |     |     | 750  |     |
| Arg | Thr | Ser | Cys | Phe  | Pro | Cys | Gly | Gly | Gly  | Leu | Ala | Thr | Lys | His  | Gln |
|     |     |     |     | 755  |     |     |     |     | 760  |     |     |     |     | 765  |     |
| Gly | Ala | Thr | Ser | Phe  | Gln | Asp | Cys | Glu | Thr  | Arg | Val | Gln | Cys | Ser  | Pro |
|     |     |     |     |      |     |     | 775 |     |      |     |     | 780 |     |      |     |
| Gly | His | Phe | Tyr | Asn  | Thr | Thr | Thr | His | Arg  | Cys | Ile | Arg | Cys | Pro  | Val |
|     |     |     |     | 790  |     |     |     |     |      |     |     | 795 |     |      | 800 |
| Gly | Thr | Tyr | Gln | Pro  | Glu | Phe | Gly | Lys | Asn  | Asn | Cys | Val | Ser | Cys  | Pro |
|     |     |     |     | 805  |     |     |     |     | 810  |     |     |     |     |      | 815 |
| Gly | Asn | Thr | Thr | Thr  | Asp | Phe | Asp | Gly | Ser  | Thr | Asn | Ile | Thr | Gln  | Cys |
|     |     |     |     | 820  |     |     |     |     | 825  |     |     |     |     | 830  |     |
| Lys | Asn | Arg | Arg | Cys  | Gly | Gly | Glu | Leu | Gly  | Asp | Phe | Thr | Gly | Tyr  | Ile |
|     |     |     |     | 835  |     |     |     | 840 |      |     |     |     | 845 |      |     |
| Glu | Ser | Pro | Asn | Tyr  | Pro | Gly | Asn | Tyr | Pro  | Ala | Asn | Thr | Glu | Cys  | Thr |
|     |     |     |     |      |     |     | 855 |     |      |     |     | 860 |     |      |     |
| Trp | Thr | Ile | Asn | Pro  | Pro | Pro | Lys | Arg | Arg  | Ile | Leu | Ile | Val | Val  | Pro |
|     |     |     |     | 870  |     |     |     |     |      |     |     | 875 |     |      | 880 |
| Glu | Ile | Phe | Leu | Pro  | Ile | Glu | Asp | Asp | Cys  | Gly | Asp | Tyr | Leu | Val  | Met |
|     |     |     |     | 885  |     |     |     |     | 890  |     |     |     |     | 895  |     |
| Arg | Lys | Thr | Ser | Ser  | Ser | Asn | Ser | Val | Thr  | Thr | Tyr | Glu | Thr | Cys  | Gln |
|     |     |     |     | 900  |     |     |     |     | 905  |     |     |     |     | 910  |     |
| Thr | Tyr | Glu | Arg | Pro  | Ile | Ala | Phe | Thr | Ser  | Arg | Ser | Lys | Lys | Leu  | Trp |
|     |     |     |     | 915  |     |     |     |     | 920  |     |     |     |     | 925  |     |
| Ile | Gln | Phe | Lys | Ser  | Asn | Glu | Gly | Asn | Ser  | Ala | Arg | Gly | Phe | Gln  | Val |
|     |     |     |     | 930  |     |     |     |     | 935  |     |     |     |     | 940  |     |
| Pro | Tyr | Val | Thr | Tyr  | Asp | Glu | Asp | Tyr | Gln  | Glu | Leu | Ile | Glu | Asp  | Ile |
|     |     |     |     | 945  |     |     |     |     | 950  |     |     |     |     | 955  | 960 |
| Val | Arg | Asp | Gly | Arg  | Leu | Tyr | Ala | Ser | Glu  | Asn | His | Gln | Glu | Ile  | Leu |
|     |     |     |     | 965  |     |     |     |     | 970  |     |     |     |     | 975  |     |
| Lys | Asp | Lys | Lys | Leu  | Ile | Lys | Ala | Leu | Phe  | Asp | Val | Leu | Ala | His  | Pro |
|     |     |     |     | 980  |     |     |     |     | 985  |     |     |     |     | 990  |     |
| Gln | Asn | Tyr | Phe | Lys  | Tyr | Thr | Ala | Gln | Glu  | Ser | Arg | Glu | Met | Phe  | Pro |
|     |     |     |     | 995  |     |     |     |     | 1000 |     |     |     |     | 1005 |     |
| Arg | Ser | Phe | Ile | Arg  | Leu | Leu | Arg | Ser | Lys  | Val | Ser | Arg | Phe | Leu  | Arg |
|     |     |     |     | 1010 |     |     |     |     | 1015 |     |     |     |     | 1020 |     |
| Pro | Tyr | Lys |     |      |     |     |     |     |      |     |     |     |     |      |     |
|     |     |     |     | 1025 |     |     |     |     |      |     |     |     |     |      |     |

<210> SEQ ID NO 61  
 <211> LENGTH: 540  
 <212> TYPE: DNA  
 <213> ORGANISM: human

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<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (41) ... (295)

<400> SEQUENCE: 61

atccctgact cgggggtgcc ttgagcag agaggaggca atg gcc acc atg gag      55
                Met Ala Thr Met Glu
                1                5

aac aag gtg atc tgc gcc ctg gtc ctg gtg tcc atg ctg gcc ctc ggc      103
Asn Lys Val Ile Cys Ala Leu Val Leu Val Ser Met Leu Ala Leu Gly
                10                15                20

acc ctg gcc gag gcc cag aca gag acg tgt aca gtg gcc ccc cgt gaa      151
Thr Leu Ala Glu Ala Gln Thr Glu Thr Cys Thr Val Ala Pro Arg Glu
                25                30                35

aga cag aat tgt ggt ttt cct ggt gtc acg ccc tcc cag tgt gca aat      199
Arg Gln Asn Cys Gly Phe Pro Gly Val Thr Pro Ser Gln Cys Ala Asn
                40                45                50

aag ggc tgc tgt ttc gac gac acc gtt cgt ggg gtc ccc tgg tgc ttc      247
Lys Gly Cys Cys Phe Asp Asp Thr Val Arg Gly Val Pro Trp Cys Phe
                55                60                65

tat cct aat acc atc gac gtc cct cca gaa gag gag tgt gaa ttt tag      295
Tyr Pro Asn Thr Ile Asp Val Pro Pro Glu Glu Glu Cys Glu Phe *
                70                75                80

acacttctgc agggatctgc ctgcatcctg acgggggtgcc gtccccagca cggtgattag      355

tcccagagct cggctgccac ctccaccgga cacctcagac acgcttctgc agctgtgcct      415

cggctcacia cacagattga ctgctctgac ttgactact caaaattggc ctaaaaatta      475

aaagagatcg atattaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa      535

aaaaa                                                                540

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<210> SEQ ID NO 62
<211> LENGTH: 84
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 62

Met Ala Thr Met Glu Asn Lys Val Ile Cys Ala Leu Val Leu Val Ser
1                5                10                15

Met Leu Ala Leu Gly Thr Leu Ala Glu Ala Gln Thr Glu Thr Cys Thr
                20                25                30

Val Ala Pro Arg Glu Arg Gln Asn Cys Gly Phe Pro Gly Val Thr Pro
                35                40                45

Ser Gln Cys Ala Asn Lys Gly Cys Cys Phe Asp Asp Thr Val Arg Gly
                50                55                60

Val Pro Trp Cys Phe Tyr Pro Asn Thr Ile Asp Val Pro Pro Glu Glu
65                70                75                80

Glu Cys Glu Phe

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<210> SEQ ID NO 63
<211> LENGTH: 590
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (28) ... (402)

<400> SEQUENCE: 63

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acctgcaccc cgcccgggca tagcacc atg cct gct tgt cgc cta ggc ccg cta      54
                Met Pro Ala Cys Arg Leu Gly Pro Leu
                1                5

gcc gcc gcc ctc ctc ctc agc ctg ctg ctg ttc ggc ttc acc cta gtc      102
Ala Ala Ala Leu Leu Leu Ser Leu Leu Leu Phe Gly Phe Thr Leu Val
10                15                20                25

tca ggc aca gga gca gag aag act ggc gtg tgc ccc gag ctc cag gct      150
Ser Gly Thr Gly Ala Glu Lys Thr Gly Val Cys Pro Glu Leu Gln Ala
                30                35                40

gac cag aac tgc acg caa gag tgc gtc tcg gac agc gaa tgc gcc gac      198
Asp Gln Asn Cys Thr Gln Glu Cys Val Ser Asp Ser Glu Cys Ala Asp
                45                50                55

aac ctc aag tgc tgc agc gcg ggc tgt gcc acc ttc tgc tct ctg ccc      246
Asn Leu Lys Cys Cys Ser Ala Gly Cys Ala Thr Phe Cys Ser Leu Pro
        60                65                70

aat gat aag gag ggt tcc tgc ccc cag gtg aac att aac ttt ccc cag      294
Asn Asp Lys Glu Gly Ser Cys Pro Gln Val Asn Ile Asn Phe Pro Gln
        75                80                85

ctc gcc ctc tgt cgg gac cag tgc cag gtg gac agc cag tgt cct ggc      342
Leu Gly Leu Cys Arg Asp Gln Cys Gln Val Asp Ser Gln Cys Pro Gly
90                95                100                105

cag atg aaa tgc tgc cgc aat ggc tgt ggg aag gtg tcc tgt gtc act      390
Gln Met Lys Cys Cys Arg Asn Gly Cys Gly Lys Val Ser Cys Val Thr
                110                115                120

ccc aat ttc tga gctccagcca ccaccaggct gagcagtgag gagagaaagt      442
Pro Asn Phe *
ttctgctg cctgcatct ggttcagcc cacctgcct ccccttttcc gggactctgt      502

attccctctt gggtgacca cagcttctcc ctttccaac caataaagta accactttca      562

gcaaaaaaaaa aaaaaaaaa aaaaaaaaa      590

```

```

<210> SEQ ID NO 64
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: human

```

```

<400> SEQUENCE: 64

```

```

Met Pro Ala Cys Arg Leu Gly Pro Leu Ala Ala Ala Leu Leu Leu Ser
1                5                10                15

Leu Leu Leu Phe Gly Phe Thr Leu Val Ser Gly Thr Gly Ala Glu Lys
20                25                30

Thr Gly Val Cys Pro Glu Leu Gln Ala Asp Gln Asn Cys Thr Gln Glu
35                40                45

Cys Val Ser Asp Ser Glu Cys Ala Asp Asn Leu Lys Cys Cys Ser Ala
50                55                60

Gly Cys Ala Thr Phe Cys Ser Leu Pro Asn Asp Lys Glu Gly Ser Cys
65                70                75                80

Pro Gln Val Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln
85                90                95

Cys Gln Val Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn
100                105                110

Gly Cys Gly Lys Val Ser Cys Val Thr Pro Asn Phe
115                120

```

```

<210> SEQ ID NO 65
<211> LENGTH: 450
<212> TYPE: DNA

```

-continued

<213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (67) ... (288)

<400> SEQUENCE: 65

```

cccaagatgg actcaggcag gcagctctgc tgtatgtgaa gcccagtggagg gggcagtgagg      60
ggggcc atg ctg cag gta caa gtt aat ctc cct gta tgc cct ctg ccc      108
      Met Leu Gln Val Gln Val Asn Leu Pro Val Ser Pro Leu Pro
      1             5             10

act tac cct tac tcc ttt ttc tac cca gat aag gag ggt tcc tgc ccc      156
Thr Tyr Pro Tyr Ser Phe Phe Tyr Pro Asp Lys Glu Gly Ser Cys Pro
15             20             25             30

cag gtg aac att aac ttt ccc cag ctg ggc ctg tgt cgg gac cag tgc      204
Gln Val Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln Cys
      35             40             45

cag gtg gac agc cag tgt cct ggc cag atg aaa tgc tgc cgc aat ggc      252
Gln Val Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn Gly
      50             55             60

tgt ggg aag gtg tcc tgt gtc act ccc aat ttc tga ggtccagcca      298
Cys Gly Lys Val Ser Cys Val Thr Pro Asn Phe *
      65             70

ccaccaggct gagcagtgag gagagaaagt ttctgcctgg ccctgcatct ggttccagcc      358
cacctgccct cccctttttc gggactctgt attccctctt gggtcgacca cagcttctcc      418
ctttccaac caataaagta accactttca gc      450

```

<210> SEQ ID NO 66  
 <211> LENGTH: 73  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 66

```

Met Leu Gln Val Gln Val Asn Leu Pro Val Ser Pro Leu Pro Thr Tyr
1             5             10             15

Pro Tyr Ser Phe Phe Tyr Pro Asp Lys Glu Gly Ser Cys Pro Gln Val
      20             25             30

Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp Gln Cys Gln Val
      35             40             45

Asp Ser Gln Cys Pro Gly Gln Met Lys Cys Cys Arg Asn Gly Cys Gly
      50             55             60

Lys Val Ser Cys Val Thr Pro Asn Phe
65             70

```

<210> SEQ ID NO 67  
 <211> LENGTH: 1595  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (81) ... (1319)

<400> SEQUENCE: 67

```

ggcagcaggc ttataacctg ggatggggcacc cctgccagtg cctgctctgc cgctgccac      60
cgctgcccga gcccagcgt atg tcc agc aaa ggc tcc gtg gtt ctg gcc tac      113
      Met Ser Ser Lys Gly Ser Val Val Leu Ala Tyr
      1             5             10

agt ggc ggc ctg gac acc tgc tgc atc ctc gtg tgg ctg aag gaa caa      161

```

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| Ser | Gly | Gly | Leu | Asp | Thr | Ser | Cys | Ile | Leu | Val | Trp | Leu | Lys | Glu | Gln |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|     |     |     | 15  |     |     |     |     | 20  |     |     |     |     | 25  |     |     |      |
| ggc | tat | gac | gtc | att | gcc | tat | ctg | gcc | aac | att | ggc | cag | aag | gaa | gac | 209  |
| Gly | Tyr | Asp | Val | Ile | Ala | Tyr | Leu | Ala | Asn | Ile | Gly | Gln | Lys | Glu | Asp |      |
|     |     | 30  |     |     |     |     | 35  |     |     |     |     | 40  |     |     |     |      |
| ttc | gag | gaa | gcc | agg | aag | aag | gca | ctg | aag | ctt | ggg | gcc | aaa | aag | gtg | 257  |
| Phe | Glu | Glu | Ala | Arg | Lys | Lys | Ala | Leu | Lys | Leu | Gly | Ala | Lys | Lys | Val |      |
|     | 45  |     |     |     |     | 50  |     |     |     | 55  |     |     |     |     |     |      |
| ttc | att | gag | gat | gtc | agc | agg | gag | ttt | gtg | gag | gag | ttc | atc | tgg | ccg | 305  |
| Phe | Ile | Glu | Asp | Val | Ser | Arg | Glu | Phe | Val | Glu | Glu | Phe | Ile | Trp | Pro |      |
| 60  |     |     |     |     | 65  |     |     |     | 70  |     |     |     |     | 75  |     |      |
| gcc | atc | cag | tcc | agc | gca | ctg | tat | gag | gac | cgc | tac | ctc | ctg | ggc | acc | 353  |
| Ala | Ile | Gln | Ser | Ser | Ala | Leu | Tyr | Glu | Asp | Arg | Tyr | Leu | Leu | Gly | Thr |      |
|     |     |     |     | 80  |     |     |     |     | 85  |     |     |     |     | 90  |     |      |
| tct | ctt | gcc | agg | ccc | tgc | atc | gcc | cgc | aaa | caa | gtg | gaa | atc | gcc | cag | 401  |
| Ser | Leu | Ala | Arg | Pro | Cys | Ile | Ala | Arg | Lys | Gln | Val | Glu | Ile | Ala | Gln |      |
|     |     |     | 95  |     |     |     |     | 100 |     |     |     |     | 105 |     |     |      |
| cgg | gag | ggg | gcc | aag | tat | gtg | tcc | cac | ggc | gcc | aca | gga | aag | ggg | aac | 449  |
| Arg | Glu | Gly | Ala | Lys | Tyr | Val | Ser | His | Gly | Ala | Thr | Gly | Lys | Gly | Asn |      |
|     |     | 110 |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |      |
| gat | cag | gtc | cgg | ttt | gag | ctc | agc | tgc | tac | tca | ctg | gcc | ccc | cag | ata | 497  |
| Asp | Gln | Val | Arg | Phe | Glu | Leu | Ser | Cys | Tyr | Ser | Leu | Ala | Pro | Gln | Ile |      |
|     | 125 |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |      |
| aag | gtc | att | gct | ccc | tgg | agg | atg | cct | gaa | ttc | tac | aac | cgg | ttc | aag | 545  |
| Lys | Val | Ile | Ala | Pro | Trp | Arg | Met | Pro | Glu | Phe | Tyr | Asn | Arg | Phe | Lys |      |
| 140 |     |     |     |     | 145 |     |     |     | 150 |     |     |     |     | 155 |     |      |
| ggc | cgc | aat | gac | ctg | atg | gag | tac | gca | aag | caa | cac | ggg | att | ccc | atc | 593  |
| Gly | Arg | Asn | Asp | Leu | Met | Glu | Tyr | Ala | Lys | Gln | His | Gly | Ile | Pro | Ile |      |
|     |     |     | 160 |     |     |     |     | 165 |     |     |     |     | 170 |     |     |      |
| ccg | gtc | act | ccc | aag | aac | ccg | tgg | agc | atg | gat | gag | aac | ctc | atg | cac | 641  |
| Pro | Val | Thr | Pro | Lys | Asn | Pro | Trp | Ser | Met | Asp | Glu | Asn | Leu | Met | His |      |
|     |     | 175 |     |     |     |     |     | 180 |     |     |     |     | 185 |     |     |      |
| atc | agc | tac | gag | gct | gga | atc | ctg | gag | aac | ccc | aag | aac | caa | gcg | cct | 689  |
| Ile | Ser | Tyr | Glu | Ala | Gly | Ile | Leu | Glu | Asn | Pro | Lys | Asn | Gln | Ala | Pro |      |
|     |     | 190 |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |      |
| cca | ggt | ctc | tac | acg | aag | acc | cag | gac | cca | gcc | aaa | gcc | ccc | aac | acc | 737  |
| Pro | Gly | Leu | Tyr | Thr | Lys | Thr | Gln | Asp | Pro | Ala | Lys | Ala | Pro | Asn | Thr |      |
|     | 205 |     |     |     |     | 210 |     |     |     | 215 |     |     |     |     |     |      |
| cct | gac | att | ctc | gag | atc | gag | ttc | aaa | aaa | ggg | gtc | cct | gtg | aag | gtg | 785  |
| Pro | Asp | Ile | Leu | Glu | Ile | Glu | Phe | Lys | Lys | Gly | Val | Pro | Val | Lys | Val |      |
| 220 |     |     |     | 225 |     |     |     |     | 230 |     |     |     | 235 |     |     |      |
| acc | aac | gtc | aag | gat | ggc | acc | acc | cac | cag | acc | tcc | ttg | gag | ctc | ttc | 833  |
| Thr | Asn | Val | Lys | Asp | Gly | Thr | Thr | His | Gln | Thr | Ser | Leu | Glu | Leu | Phe |      |
|     |     |     | 240 |     |     |     |     |     | 245 |     |     |     | 250 |     |     |      |
| atg | tac | ctg | aac | gaa | gtc | gcg | ggc | aag | cat | ggc | gtg | ggc | cgt | att | gac | 881  |
| Met | Tyr | Leu | Asn | Glu | Val | Ala | Gly | Lys | His | Gly | Val | Gly | Arg | Ile | Asp |      |
|     |     | 255 |     |     |     |     | 260 |     |     |     |     |     | 265 |     |     |      |
| atc | gtg | gag | aac | cgc | ttc | att | gga | atg | aag | tcc | cga | ggt | atc | tac | gag | 929  |
| Ile | Val | Glu | Asn | Arg | Phe | Ile | Gly | Met | Lys | Ser | Arg | Gly | Ile | Tyr | Glu |      |
|     |     | 270 |     |     |     | 275 |     |     |     |     |     | 280 |     |     |     |      |
| acc | cca | gca | ggc | acc | atc | ctt | tac | cac | gct | cat | tta | gac | atc | gag | gcc | 977  |
| Thr | Pro | Ala | Gly | Thr | Ile | Leu | Tyr | His | Ala | His | Leu | Asp | Ile | Glu | Ala |      |
|     |     | 285 |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     |      |
| ttc | acc | atg | gac | cgg | gaa | gtg | cgc | aaa | atc | aaa | caa | ggc | ctg | ggc | ttg | 1025 |
| Phe | Thr | Met | Asp | Arg | Glu | Val | Arg | Lys | Ile | Lys | Gln | Gly | Leu | Gly | Leu |      |
| 300 |     |     |     | 305 |     |     |     |     | 310 |     |     |     | 315 |     |     |      |
| aaa | ttt | gct | gag | ctg | gtg | tat | acc | ggt | ttc | tgg | cac | agc | cct | gag | tgt | 1073 |

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|            |             |            |             |            |            |            |     |     |     |     |     |     |     |     |     |      |
|------------|-------------|------------|-------------|------------|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Lys        | Phe         | Ala        | Glu         | Leu        | Val        | Tyr        | Thr | Gly | Phe | Trp | His | Ser | Pro | Glu | Cys |      |
|            |             |            |             | 320        |            |            |     |     | 325 |     |     |     |     | 330 |     |      |
| gaa        | ttt         | gtc        | cgc         | cac        | tgc        | atc        | gcc | aag | tcc | cag | gag | cga | gtg | gaa | ggg | 1121 |
| Glu        | Phe         | Val        | Arg         | His        | Cys        | Ile        | Ala | Lys | Ser | Gln | Glu | Arg | Val | Glu | Gly |      |
|            |             |            | 335         |            |            |            |     | 340 |     |     |     |     | 345 |     |     |      |
| aaa        | gtg         | cag        | gtg         | tcc        | gtc        | ctc        | aag | ggc | cag | gtg | tac | atc | ctc | ggc | cgg | 1169 |
| Lys        | Val         | Gln        | Val         | Ser        | Val        | Leu        | Lys | Gly | Gln | Val | Tyr | Ile | Leu | Gly | Arg |      |
|            |             |            | 350         |            |            |            | 355 |     |     |     |     | 360 |     |     |     |      |
| gag        | tcc         | cca        | ctg         | tct        | ctc        | tac        | aat | gag | gag | ctg | gtg | agc | atg | aac | gtg | 1217 |
| Glu        | Ser         | Pro        | Leu         | Ser        | Leu        | Tyr        | Asn | Glu | Glu | Leu | Val | Ser | Met | Asn | Val |      |
|            |             |            | 365         |            |            | 370        |     |     |     |     | 375 |     |     |     |     |      |
| cag        | ggt         | gat        | tat         | gag        | cca        | act        | gat | gcc | acc | ggg | ttc | atc | aac | atc | aat | 1265 |
| Gln        | Gly         | Asp        | Tyr         | Glu        | Pro        | Thr        | Asp | Ala | Thr | Gly | Phe | Ile | Asn | Ile | Asn |      |
|            |             |            |             |            | 385        |            |     |     |     | 390 |     |     |     |     | 395 |      |
| tcc        | ctc         | agg        | ctg         | aag        | gaa        | tat        | cat | cgt | ctc | cag | agc | aag | gtc | act | gcc | 1313 |
| Ser        | Leu         | Arg        | Leu         | Lys        | Glu        | Tyr        | His | Arg | Leu | Gln | Ser | Lys | Val | Thr | Ala |      |
|            |             |            |             | 400        |            |            |     |     | 405 |     |     |     |     | 410 |     |      |
| aaa        | tag         | acccgtgtac | aatgaggagc  | tggggcctcc | tcaatttgca | gatcccccaa |     |     |     |     |     |     |     |     |     | 1369 |
| Lys        | *           |            |             |            |            |            |     |     |     |     |     |     |     |     |     |      |
| gtacaggcgc | taattgttgt  | gataatttgt | aattgtgact  | tgttctcccc | ggctggcagc |            |     |     |     |     |     |     |     |     |     | 1429 |
| gtagtggggc | tgccaggccc  | cagcttttgt | ccctgggtccc | cctgaagcct | gcaaacgttg |            |     |     |     |     |     |     |     |     |     | 1489 |
| tcacgaagg  | gaaggggtggg | gggcagctgc | ggtgggggagc | tataaaaatg | acaattaaaa |            |     |     |     |     |     |     |     |     |     | 1549 |
| gagacactag | tcttttattt  | ctaaaaaaaa | aaaaaaaaaa  | aaaaaa     |            |            |     |     |     |     |     |     |     |     |     | 1595 |

&lt;210&gt; SEQ ID NO 68

&lt;211&gt; LENGTH: 412

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 68

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Ser | Lys | Gly | Ser | Val | Val | Leu | Ala | Tyr | Ser | Gly | Gly | Leu | Asp |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Thr | Ser | Cys | Ile | Leu | Val | Trp | Leu | Lys | Glu | Gln | Gly | Tyr | Asp | Val | Ile |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Ala | Tyr | Leu | Ala | Asn | Ile | Gly | Gln | Lys | Glu | Asp | Phe | Glu | Glu | Ala | Arg |
|     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Lys | Lys | Ala | Leu | Lys | Leu | Gly | Ala | Lys | Lys | Val | Phe | Ile | Glu | Asp | Val |
|     |     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Ser | Arg | Glu | Phe | Val | Glu | Glu | Phe | Ile | Trp | Pro | Ala | Ile | Gln | Ser | Ser |
|     |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Ala | Leu | Tyr | Glu | Asp | Arg | Tyr | Leu | Leu | Gly | Thr | Ser | Leu | Ala | Arg | Pro |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Cys | Ile | Ala | Arg | Lys | Gln | Val | Glu | Ile | Ala | Gln | Arg | Glu | Gly | Ala | Lys |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Tyr | Val | Ser | His | Gly | Ala | Thr | Gly | Lys | Gly | Asn | Asp | Gln | Val | Arg | Phe |
|     |     |     | 115 |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Glu | Leu | Ser | Cys | Tyr | Ser | Leu | Ala | Pro | Gln | Ile | Lys | Val | Ile | Ala | Pro |
|     |     |     | 130 |     |     |     | 135 |     |     |     | 140 |     |     |     |     |
| Trp | Arg | Met | Pro | Glu | Phe | Tyr | Asn | Arg | Phe | Lys | Gly | Arg | Asn | Asp | Leu |
|     |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Met | Glu | Tyr | Ala | Lys | Gln | His | Gly | Ile | Pro | Ile | Pro | Val | Thr | Pro | Lys |
|     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Asn | Pro | Trp | Ser | Met | Asp | Glu | Asn | Leu | Met | His | Ile | Ser | Tyr | Glu | Ala |
|     |     |     |     | 180 |     |     |     | 185 |     |     |     |     |     | 190 |     |

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Gly Ile Leu Glu Asn Pro Lys Asn Gln Ala Pro Pro Gly Leu Tyr Thr  
 195 200 205  
 Lys Thr Gln Asp Pro Ala Lys Ala Pro Asn Thr Pro Asp Ile Leu Glu  
 210 215 220  
 Ile Glu Phe Lys Lys Gly Val Pro Val Lys Val Thr Asn Val Lys Asp  
 225 230 235 240  
 Gly Thr Thr His Gln Thr Ser Leu Glu Leu Phe Met Tyr Leu Asn Glu  
 245 250 255  
 Val Ala Gly Lys His Gly Val Gly Arg Ile Asp Ile Val Glu Asn Arg  
 260 265 270  
 Phe Ile Gly Met Lys Ser Arg Gly Ile Tyr Glu Thr Pro Ala Gly Thr  
 275 280 285  
 Ile Leu Tyr His Ala His Leu Asp Ile Glu Ala Phe Thr Met Asp Arg  
 290 295 300  
 Glu Val Arg Lys Ile Lys Gln Gly Leu Gly Leu Lys Phe Ala Glu Leu  
 305 310 315 320  
 Val Tyr Thr Gly Phe Trp His Ser Pro Glu Cys Glu Phe Val Arg His  
 325 330 335  
 Cys Ile Ala Lys Ser Gln Glu Arg Val Glu Gly Lys Val Gln Val Ser  
 340 345 350  
 Val Leu Lys Gly Gln Val Tyr Ile Leu Gly Arg Glu Ser Pro Leu Ser  
 355 360 365  
 Leu Tyr Asn Glu Glu Leu Val Ser Met Asn Val Gln Gly Asp Tyr Glu  
 370 375 380  
 Pro Thr Asp Ala Thr Gly Phe Ile Asn Ile Asn Ser Leu Arg Leu Lys  
 385 390 395 400  
 Glu Tyr His Arg Leu Gln Ser Lys Val Thr Ala Lys  
 405 410

<210> SEQ ID NO 69  
 <211> LENGTH: 2682  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (18) ... (980)

<400> SEQUENCE: 69

cgagccaggg agaaagg atg gcc ggc ctg gcg gcg cgg ttg gtc ctg cta 50  
 Met Ala Gly Leu Ala Ala Arg Leu Val Leu Leu  
 1 5 10  
 gct ggg gca gcg gcg ctg gcg agc ggc tcc cag ggc gac cgt gag ccg 98  
 Ala Gly Ala Ala Ala Leu Ala Ser Gly Ser Gln Gly Asp Arg Glu Pro  
 15 20 25  
 gtg tac cgc gac tgc gta ctg cag tgc gaa gag cag aac tgc tct ggg 146  
 Val Tyr Arg Asp Cys Val Leu Gln Cys Glu Glu Gln Asn Cys Ser Gly  
 30 35 40  
 ggc gct ctg aat cac ttc cgc tcc cgc cag cca atc tac atg agt cta 194  
 Gly Ala Leu Asn His Phe Arg Ser Arg Gln Pro Ile Tyr Met Ser Leu  
 45 50 55  
 gca ggc tgg acc tgt cgg gac gac tgt aag tat gag tgt atg tgg gtc 242  
 Ala Gly Trp Thr Cys Arg Asp Asp Cys Lys Tyr Glu Cys Met Trp Val  
 60 65 70 75  
 acc gtt ggg ctc tac ctc cag gaa ggt cac aaa gtg cct cag ttc cat 290  
 Thr Val Gly Leu Tyr Leu Gln Glu Gly His Lys Val Pro Gln Phe His

|                                                                   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|-------------------------------------------------------------------|-----|--|--|--|--|-----|--|--|--|--|-----|--|--|--|--|------|
|                                                                   | 80  |  |  |  |  | 85  |  |  |  |  | 90  |  |  |  |  |      |
| ggc aag tgg ccc ttc tcc cgg ttc ctg ttc ttt caa gag ccg gca tcg   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 338  |
| Gly Lys Trp Pro Phe Ser Arg Phe Leu Phe Phe Gln Glu Pro Ala Ser   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 95  |  |  |  |  | 100 |  |  |  |  | 105 |  |  |  |  |      |
| gcc gtg gcc tcg ttt ctc aat ggc ctg gcc agc ctg gtg atg ctc tgc   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 386  |
| Ala Val Ala Ser Phe Leu Asn Gly Leu Ala Ser Leu Val Met Leu Cys   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 110 |  |  |  |  | 115 |  |  |  |  | 120 |  |  |  |  |      |
| cgc tac cgc acc ttc gtg cca gcc tcc tcc ccc atg tac cac acc tgt   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 434  |
| Arg Tyr Arg Thr Phe Val Pro Ala Ser Ser Pro Met Tyr His Thr Cys   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 125 |  |  |  |  | 130 |  |  |  |  | 135 |  |  |  |  |      |
| gtg gcc ttc gcc tgg gtg tcc ctc aat gca tgg ttc tgg tcc aca gtt   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 482  |
| Val Ala Phe Ala Trp Val Ser Leu Asn Ala Trp Phe Trp Ser Thr Val   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 140 |  |  |  |  | 145 |  |  |  |  | 150 |  |  |  |  |      |
| ttc cac acc agg gac act gac ctc aca gag aaa atg gac tac ttc tgt   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 530  |
| Phe His Thr Arg Asp Thr Asp Leu Thr Glu Lys Met Asp Tyr Phe Cys   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 160 |  |  |  |  | 165 |  |  |  |  | 170 |  |  |  |  |      |
| gcc tcc act gtc atc cta cac tca atc tac ctg tgc tgc gtc agg acc   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 578  |
| Ala Ser Thr Val Ile Leu His Ser Ile Tyr Leu Cys Cys Val Arg Thr   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 175 |  |  |  |  | 180 |  |  |  |  | 185 |  |  |  |  |      |
| gtg ggg ctg cag cac cca gct gtg gtc agt gcc ttc cgg gct ctc ctg   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 626  |
| Val Gly Leu Gln His Pro Ala Val Val Ser Ala Phe Arg Ala Leu Leu   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 190 |  |  |  |  | 195 |  |  |  |  | 200 |  |  |  |  |      |
| ctg ctc atg ctg acc gtg cac gtc tcc tac ctg agc ctc atc cgc ttc   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 674  |
| Leu Leu Met Leu Thr Val His Val Ser Tyr Leu Ser Leu Ile Arg Phe   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 205 |  |  |  |  | 210 |  |  |  |  | 215 |  |  |  |  |      |
| gac tat ggc tac aac ctg gtg gcc aac gtg gct att ggc ctg gtc aac   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 722  |
| Asp Tyr Gly Tyr Asn Leu Val Ala Asn Val Ala Ile Gly Leu Val Asn   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 220 |  |  |  |  | 225 |  |  |  |  | 230 |  |  |  |  |      |
| gtg gtg tgg tgg ctg gcc tgg tgc ctg tgg aac cag cgg cgg ctg cct   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 770  |
| Val Val Trp Trp Leu Ala Trp Cys Leu Trp Asn Gln Arg Arg Leu Pro   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 240 |  |  |  |  | 245 |  |  |  |  | 250 |  |  |  |  |      |
| cac gtg cgc aag tgc gtg gtg gtg gtc ttg ctg ctg cag ggg ctg tcc   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 818  |
| His Val Arg Lys Cys Val Val Val Val Leu Leu Leu Gln Gly Leu Ser   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 255 |  |  |  |  | 260 |  |  |  |  | 265 |  |  |  |  |      |
| ctg ctc gag ctg ctt gac ttc cca ccg ctc ttc tgg gtc ctg gat gcc   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 866  |
| Leu Leu Glu Leu Leu Asp Phe Pro Pro Leu Phe Trp Val Leu Asp Ala   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 270 |  |  |  |  | 275 |  |  |  |  | 280 |  |  |  |  |      |
| cat gcc atc tgg cac atc agc acc atc cct gtc cac gtc ctc ttt ttc   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 914  |
| His Ala Ile Trp His Ile Ser Thr Ile Pro Val His Val Leu Phe Phe   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 285 |  |  |  |  | 290 |  |  |  |  | 295 |  |  |  |  |      |
| agc ttt ctg gaa gat gac agc ctg tac ctg ctg aag gaa tca gag gac   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 962  |
| Ser Phe Leu Glu Asp Asp Ser Leu Tyr Leu Leu Lys Glu Ser Glu Asp   |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 300 |  |  |  |  | 305 |  |  |  |  | 310 |  |  |  |  |      |
| aag ttc aag ctg gac tga agaccttgga gcgagtctgc cccagtgggg          |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1010 |
| Lys Phe Lys Leu Asp *                                             |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
|                                                                   | 320 |  |  |  |  |     |  |  |  |  |     |  |  |  |  |      |
| atcctgcccc cgccctgctg gcctcccttc tccctcaac ccttgagatg attttctctt  |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1070 |
| ttcaacttct tgaacttgga catgaaggat gtgggcccag aatcatgtgg ccagcccacc |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1130 |
| ccctgttggc cctcaccagc cttggagtct gttctaggga aggcctccca gcatctggga |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1190 |
| ctcgagagtg ggcagcccct ctacctctg gagctgaact ggggtggaac tgagtgtgct  |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1250 |
| cttagctcta ccgggaggac agctgcctgt ttctctccca tcagcctcct cccacatcc  |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1310 |
| ccagctgcct ggctgggtgc tgaagccctc tgtctacctg ggagaccagg gaccacaggc |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1370 |
| cttaqqgata caqqqqgtcc ccttctqgta ccacccccca cctctctcca qqacaccact |     |  |  |  |  |     |  |  |  |  |     |  |  |  |  | 1430 |

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aggtggtgct ggatgcttgt tctttggcca gccaaaggttc acggcgattc tccccatggg 1490
atcttgaggg accaagctgc tgggattggg aaggagtttc accctgacca ttgccctagc 1550
cagggtccca ggaggcctca ccatactccc tttcagggcc agggctccag caagcccagg 1610
gcaaggatcc tgtgctgctg tctggttgag agcctgccac cgtgtgtcgg gagtgtgggc 1670
caggctgagt gcataggta cagggccgtg agcatgggcc tgggtgtgtg tgagctcagg 1730
cctaggtgcg cagtgtggag acgggtgttg tcggggaaga ggtgtggctt caaagtgtgt 1790
gtgtgcaggg ggtgggtgtg ttagcgtggg ttaggggaac gtgtgtgcgc gtgctgggtg 1850
gcatgtgaga tgagtactg ccggtgaatg tgccacagt tgagaggttg gagcaggatg 1910
aggaatcct gtcaccatca ataatcactt gtggagcgcc agctctgccc aaggcgccac 1970
ctgggcggac agccaggagc tctccatggc caggctgcct gtgtgcatgt tccctgtctg 2030
gtgccccctt gccgcctcc tgcaaacctc acagggtccc cacacaacag tgccctccag 2090
aagcagcccc tcggaggcag aggaaggaaa atggggatgg ctggggctct ctccatcctc 2150
ctttctcct tgcttcgca tggctggcct tccccccaa aacctccatt cccctgctgc 2210
cagccccctt gccatagcct gatattgggg aggaggaagg ggcgatttga gggagaaggg 2270
gagaaagctt atggctgggt ctggtttctt ccctccag aggtcttac tgtccaggg 2330
tgccccagg gcaggcagg gccacactat gctgcgccc tggtaaagg gacccctgcc 2390
attaccagc agccctggca tgttcctgcc ccacaggaat agaatggagg gagctccaga 2450
aactttccat cccaaaggca gtctccgtgg ttgaagcaga ctggattttt gctctgcccc 2510
tgaccccttg tccctcttg agggagggga gctatgctag gactccaacc tcagggactc 2570
gggtggcctg cgctagcttc ttttgatact gaaaactttt aaggtgggag ggtggcaagg 2630
gatgtgctta ataaatcaat tccaagcctc aaaaaaaaaa aaaaaaaaaa aa 2682

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&lt;210&gt; SEQ ID NO 70

&lt;211&gt; LENGTH: 320

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 70

```

Met Ala Gly Leu Ala Ala Arg Leu Val Leu Leu Ala Gly Ala Ala Ala
1           5           10          15
Leu Ala Ser Gly Ser Gln Gly Asp Arg Glu Pro Val Tyr Arg Asp Cys
20          25          30
Val Leu Gln Cys Glu Glu Gln Asn Cys Ser Gly Gly Ala Leu Asn His
35          40          45
Phe Arg Ser Arg Gln Pro Ile Tyr Met Ser Leu Ala Gly Trp Thr Cys
50          55          60
Arg Asp Asp Cys Lys Tyr Glu Cys Met Trp Val Thr Val Gly Leu Tyr
65          70          75          80
Leu Gln Glu Gly His Lys Val Pro Gln Phe His Gly Lys Trp Pro Phe
85          90          95
Ser Arg Phe Leu Phe Phe Gln Glu Pro Ala Ser Ala Val Ala Ser Phe
100         105         110
Leu Asn Gly Leu Ala Ser Leu Val Met Leu Cys Arg Tyr Arg Thr Phe
115         120         125
Val Pro Ala Ser Ser Pro Met Tyr His Thr Cys Val Ala Phe Ala Trp
130         135         140

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Leu | Asn | Ala | Trp | Phe | Trp | Ser | Thr | Val | Phe | His | Thr | Arg | Asp |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Thr | Asp | Leu | Thr | Glu | Lys | Met | Asp | Tyr | Phe | Cys | Ala | Ser | Thr | Val | Ile |
|     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     | 175 |     |
| Leu | His | Ser | Ile | Tyr | Leu | Cys | Cys | Val | Arg | Thr | Val | Gly | Leu | Gln | His |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Pro | Ala | Val | Val | Ser | Ala | Phe | Arg | Ala | Leu | Leu | Leu | Leu | Met | Leu | Thr |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     |     | 205 |     |     |
| Val | His | Val | Ser | Tyr | Leu | Ser | Leu | Ile | Arg | Phe | Asp | Tyr | Gly | Tyr | Asn |
|     | 210 |     |     |     |     |     | 215 |     |     |     | 220 |     |     |     |     |
| Leu | Val | Ala | Asn | Val | Ala | Ile | Gly | Leu | Val | Asn | Val | Val | Trp | Trp | Leu |
| 225 |     |     |     | 230 |     |     |     |     |     | 235 |     |     |     |     | 240 |
| Ala | Trp | Cys | Leu | Trp | Asn | Gln | Arg | Arg | Leu | Pro | His | Val | Arg | Lys | Cys |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Val | Val | Val | Val | Leu | Leu | Leu | Gln | Gly | Leu | Ser | Leu | Leu | Glu | Leu | Leu |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Asp | Phe | Pro | Pro | Leu | Phe | Trp | Val | Leu | Asp | Ala | His | Ala | Ile | Trp | His |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Ile | Ser | Thr | Ile | Pro | Val | His | Val | Leu | Phe | Phe | Ser | Phe | Leu | Glu | Asp |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Asp | Ser | Leu | Tyr | Leu | Leu | Lys | Glu | Ser | Glu | Asp | Lys | Phe | Lys | Leu | Asp |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |

&lt;210&gt; SEQ ID NO 71

&lt;211&gt; LENGTH: 2116

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: human

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: CDS

&lt;222&gt; LOCATION: (57) ... (299)

&lt;400&gt; SEQUENCE: 71

|                                                                     |     |
|---------------------------------------------------------------------|-----|
| cggttctcca agcaccacgc atcctgctag acgcgccgcg caccgacgga ggggac atg   | 59  |
| Met                                                                 |     |
| 1                                                                   |     |
| ggc aga gca atg gtg gcc agg ctg ggg ctg ggg ctg ctg ctg gca         | 107 |
| Gly Arg Ala Met Val Ala Arg Leu Gly Leu Leu Leu Leu Ala             |     |
| 5 10 15                                                             |     |
| ctg ctc cta ccc acg cag att tat tcc agt gaa aca aca act gga act     | 155 |
| Leu Leu Leu Pro Thr Gln Ile Tyr Ser Ser Glu Thr Thr Thr Gly Thr     |     |
| 20 25 30                                                            |     |
| tca agt aac tcc tcc cag agt act tcc aac tct ggg ttg gcc cca aat     | 203 |
| Ser Ser Asn Ser Ser Gln Ser Thr Ser Asn Ser Gly Leu Ala Pro Asn     |     |
| 35 40 45                                                            |     |
| cca act aat gcc acc acc aag gcg gct ggt ggt gcc ctg cag tca aca     | 251 |
| Pro Thr Asn Ala Thr Thr Lys Ala Ala Gly Gly Ala Leu Gln Ser Thr     |     |
| 50 55 60 65                                                         |     |
| gcc agt ctc ttc gtg gtc tca ctc tct ctt ctg cat ctc tac tct taa     | 299 |
| Ala Ser Leu Phe Val Val Ser Leu Ser Leu Leu His Leu Tyr Ser *       |     |
| 70 75 80                                                            |     |
| gagactcagg ccaagaaacg tcttctaaat ttcccatct tctaaacca atccaaatgg     | 359 |
| cgtctggaag tccaatgtgg caaggaaaaa caggtcttca tcgaatctac taattccaca   | 419 |
| ccttttattg acacagaaaa tggtgagaat cccaaatttg attgatttga agaacatgtg   | 479 |
| agaggtttga ctagatgatg aatgccaaata ttaaactctgc tggagtttca tgtacaagat | 539 |

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gaaggagagg caacatccaa aatagttaag acatgatttc cttgaatgtg gcttgagaaa 599
tatggacact taatactacc ttgaaaataa gaatagaaat aaaggatggg attgtggaat 659
ggagattcag ttttcattgg ttcattaatt ctataaggcc ataaaacagg taatataaaa 719
agcttcctac gatctattta tatgtacatg agaaggaatc cccagggtgtt actgtaattc 779
ctcaacgtat tgtttcgacg gcactaatTT aatgccgata tactctagat gaatgtttac 839
attgttgagc tattgtgtgt ctcttgggaa ctgaactcac tttcctcctg aggcctttgga 899
tttgacattg catttgacct tttaggtagt aattgacatg tgccagggca atgatgaatg 959
agaatctacc ccagatccaa gcactcctgag caactcctga ttatccatat tgaagcaaat 1019
ggtaggcatt tcctatcacc tgtttccatt caacaagagc actacattct tttagctaaa 1079
cggattccaa agagtagaat tgcattgacc acgactaatt tcaaaatgct ttttattatt 1139
attatTTTT agacagtctc actttgtcgc ccaggccgga gtgcagtggg gcgatctcag 1199
atcagtgtac catttgcctc ccgggctcaa gcgattctcc tgctcagcc tcccaagtag 1259
ctgggattac aggcacctgc caccatgccc ggctaatttt tgtaatttta gtagagacag 1319
ggtttcacca tgttgcccag gctggtttag aactcctgac ctcagggtgat ccacccgcct 1379
cggcctccca aagtgtctggg attacaggct tgagcccccg cgcccagcca tcaaaatgct 1439
ttttatttct gcatatgttt gaatactttt tacaatttaa aaaaatgatc tgttttgaag 1499
gcaaaattgc aaatcttgaa attaagaagg caaaatgtaa aggagtcaaa ctataaatca 1559
agtatttggg aagtgaagac tggaagctaa tttgcataaa ttcacaaact tttatactct 1619
ttctgtatat acattttttt tctttaaaaa acaactatgg atcagaatag caacatttag 1679
aacacttttt gttatcagtc aatattttta gatagttaga acctggctct aagcctaaaa 1739
gtgggcttga ttctgcagta aatcttttac aactgcctcg acacacataa acctttttaa 1799
aaatagacac tccccgaagt cttttgtttg tatggtcaca cactgatgct tagatgttcc 1859
agtaatctaa tatggccaca gtagtcttga tgaccaaagt cctttttttc catctttaga 1919
aaactacatg ggaacaaaca gatcgaacag ttttgaagct actgtgtgtg tgaatgaaca 1979
ctcttgcttt attccagaat gctgtacatc tattttggat tgtatattgt ggttgtgtat 2039
ttacgctttg attcatagta acttcttatg gaattgattt gcattgaacg acaaaactga 2099
aataaaaaga aacgggtg 2116

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<210> SEQ ID NO 72
<211> LENGTH: 80
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 72

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```

Met Gly Arg Ala Met Val Ala Arg Leu Gly Leu Gly Leu Leu Leu Leu
1           5           10          15
Ala Leu Leu Leu Pro Thr Gln Ile Tyr Ser Ser Glu Thr Thr Thr Gly
20          25          30
Thr Ser Ser Asn Ser Ser Gln Ser Thr Ser Asn Ser Gly Leu Ala Pro
35          40          45
Asn Pro Thr Asn Ala Thr Thr Lys Ala Ala Gly Gly Ala Leu Gln Ser
50          55          60
Thr Ala Ser Leu Phe Val Val Ser Leu Ser Leu Leu His Leu Tyr Ser

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| 65                                                                                                                                                               | 70  | 75  | 80  |      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|------|
| <210> SEQ ID NO 73<br><211> LENGTH: 1513<br><212> TYPE: DNA<br><213> ORGANISM: human<br><220> FEATURE:<br><221> NAME/KEY: CDS<br><222> LOCATION: (236) ... (742) |     |     |     |      |
| <400> SEQUENCE: 73                                                                                                                                               |     |     |     |      |
| attcacttct cacaaggact ggggtgaagag ttctgcagcc ttacagagac tggaaaagaa                                                                                               |     |     |     | 60   |
| gccccaaacca aggcccccag agaggtcccc caggccccctt tgggtccctg agcctcagct                                                                                              |     |     |     | 120  |
| ggaggtgggg ggtgcctgca gtgcgtggc tcagtctcct tctgaaaagc tggatccagc                                                                                                 |     |     |     | 180  |
| ttgtttgaag cccttgagct gatcttagat cggcgcagg agaccaacgc ctgcc atg                                                                                                  |     |     |     | 238  |
|                                                                                                                                                                  |     |     | Met |      |
|                                                                                                                                                                  |     |     | 1   |      |
| ctg ttc cgg ctc tca gag cac tcc tca cca gag gag gaa gcc tcc ccc                                                                                                  |     |     |     | 286  |
| Leu Phe Arg Leu Ser Glu His Ser Ser Pro Glu Glu Glu Ala Ser Pro                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 5   | 10  | 15  |      |
| cac cag aga gcc tca gga gag ggg cac cat ctc aag tcg aag aga ccc                                                                                                  |     |     |     | 334  |
| His Gln Arg Ala Ser Gly Glu Gly His His Leu Lys Ser Lys Arg Pro                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 20  | 25  | 30  |      |
| aac ccc tgt gcc tac aca cca cct tcg ctg aaa gct gtg cag cgc att                                                                                                  |     |     |     | 382  |
| Asn Pro Cys Ala Tyr Thr Pro Pro Ser Leu Lys Ala Val Gln Arg Ile                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 35  | 40  | 45  |      |
| gct gag tct cac ctg cag tct atc agc aat ttg aat gag aac cag gcc                                                                                                  |     |     |     | 430  |
| Ala Glu Ser His Leu Gln Ser Ile Ser Asn Leu Asn Glu Asn Gln Ala                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 50  | 55  | 60  | 65   |
| tca gag gag gag gat gag ctg ggg gag ctt cgg gag ctg ggt tat cca                                                                                                  |     |     |     | 478  |
| Ser Glu Glu Glu Asp Glu Leu Gly Glu Leu Arg Glu Leu Gly Tyr Pro                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 70  | 75  | 80  |      |
| aga gag gaa gat gag gag gaa gag gat gat gaa gaa gag gaa gaa                                                                                                      |     |     |     | 526  |
| Arg Glu Glu Asp Glu Glu Glu Glu Asp Asp Glu Glu Glu Glu Glu                                                                                                      |     |     |     |      |
|                                                                                                                                                                  | 85  | 90  | 95  |      |
| gaa gag gac agc cag gct gaa gtc ctg aag gtc atc agg cag tct gct                                                                                                  |     |     |     | 574  |
| Glu Glu Asp Ser Gln Ala Glu Val Leu Lys Val Ile Arg Gln Ser Ala                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 100 | 105 | 110 |      |
| ggg caa aag aca acc tgt ggc cag ggt ctg gaa ggg ccc tgg gag cgc                                                                                                  |     |     |     | 622  |
| Gly Gln Lys Thr Thr Cys Gly Gln Gly Leu Glu Gly Pro Trp Glu Arg                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 115 | 120 | 125 |      |
| cca ccc cct ctg gat gag tcc gag aga gat gga ggc tct gag gac caa                                                                                                  |     |     |     | 670  |
| Pro Pro Pro Leu Asp Glu Ser Glu Arg Asp Gly Gly Ser Glu Asp Gln                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 130 | 135 | 140 | 145  |
| gtg gaa gac cca gca cta agt gag cct ggg gag gaa cct cag cgc cct                                                                                                  |     |     |     | 718  |
| Val Glu Asp Pro Ala Leu Ser Glu Pro Gly Glu Glu Pro Gln Arg Pro                                                                                                  |     |     |     |      |
|                                                                                                                                                                  | 150 | 155 | 160 |      |
| tcc ccc tct gag cct ggc aca tag gcacccagcc tgcattctccc aggaggaagt                                                                                                |     |     |     | 772  |
| Ser Pro Ser Glu Pro Gly Thr *                                                                                                                                    |     |     |     |      |
|                                                                                                                                                                  | 165 |     |     |      |
| ggaggggaca tcgtgtttcc ccagaaaccc actctatect caccctgttt tgtgtctttc                                                                                                |     |     |     | 832  |
| ccctgcctg ctagggtgac ggcttctgac ttctagaaga ctaaggctgg tctgtgtttg                                                                                                 |     |     |     | 892  |
| cttgttttgc cacccttggc tgataccag agaacctggg cacttgctgc ctgatgccca                                                                                                 |     |     |     | 952  |
| ccctgcagc tcattctccc attcaccag cgggaggtgg gatgtgagac agccacatt                                                                                                   |     |     |     | 1012 |
| ggaaaatcca gaaaaccggg aacagggtatt tgccttcac aattctactc ccagatcct                                                                                                 |     |     |     | 1072 |

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ctccccctgga cacaggagac ccacagggca ggaccctaag atctggggaa aggaggtcct 1132
gagaaccttg aggtaccctt agatcctttt ctaccactt tcctatggag gattccaagt 1192
caccacttct ctcaccggct tctaccaggg tccaggacta aggcgttttt ctccatagcc 1252
tcaacatttt gggaatcttc ccttaatcac ccttgctcct cctgggtgcc tggaagatgg 1312
actggcagag acctctttgt tgcgttttgt gctttgatgc caggaatgcc gcctagttta 1372
tgtccccggt ggggcacaca gcggggggcg ccaggttttc cttgtcccc agctgctctg 1432
ccccctttccc cttcttcctt gactccaggc ctgaaccctt cccgtgctgt aataaatctt 1492
tgtaaataac aaaaaaaaaa a 1513

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<210> SEQ ID NO 74
<211> LENGTH: 168
<212> TYPE: PRT
<213> ORGANISM: human

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```

<400> SEQUENCE: 74

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```

Met Leu Phe Arg Leu Ser Glu His Ser Ser Pro Glu Glu Glu Ala Ser
1      5      10      15
Pro His Gln Arg Ala Ser Gly Glu Gly His His Leu Lys Ser Lys Arg
20     25     30
Pro Asn Pro Cys Ala Tyr Thr Pro Ser Leu Lys Ala Val Gln Arg
35     40     45
Ile Ala Glu Ser His Leu Gln Ser Ile Ser Asn Leu Asn Glu Asn Gln
50     55     60
Ala Ser Glu Glu Glu Asp Glu Leu Gly Glu Leu Arg Glu Leu Gly Tyr
65     70     75     80
Pro Arg Glu Glu Asp Glu Glu Glu Glu Glu Asp Asp Glu Glu Glu
85     90     95
Glu Glu Glu Asp Ser Gln Ala Glu Val Leu Lys Val Ile Arg Gln Ser
100    105    110
Ala Gly Gln Lys Thr Thr Cys Gly Gln Gly Leu Glu Gly Pro Trp Glu
115    120    125
Arg Pro Pro Pro Leu Asp Glu Ser Glu Arg Asp Gly Gly Ser Glu Asp
130    135    140
Gln Val Glu Asp Pro Ala Leu Ser Glu Pro Gly Glu Glu Pro Gln Arg
145    150    155    160
Pro Ser Pro Ser Glu Pro Gly Thr
165

```

```

<210> SEQ ID NO 75
<211> LENGTH: 1841
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (468)...(1082)

```

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<400> SEQUENCE: 75

```

```

agctgggacc ggagggtgag cccggcagag gcagagacac acgcggagag gaggagaggc 60
tgaggggagg aggtggagaa ggacgggaga ggcagagaga ggagacacgc agagacactc 120
aggaggggag agacaccgag acgcagagac actcaggagg ggagagacac cgagacgcag 180
agacaccag gccgggggagc gcgaggggagc gaggcacaga cctggctcag cgagcgcggg 240

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|                                                                   |      |
|-------------------------------------------------------------------|------|
| gggcgagccc cgagtcgccg gagcctgggg gcgcgcccag cccgggcgcc gaccctcctc | 300  |
| ccgctcccgc gccctcccct cggcgggcac ggtattttta tccgtgcgag aacagccctc | 360  |
| ctcctcctct cgccgcacag cccgcgcct gcgcggggga gcccagcaca gaccgcgcgc  | 420  |
| gggaccccga gtgcgcaccc ccagccccc cgccccccc gcgcgcc atg gac ccc     | 476  |
| Met Asp Pro                                                       |      |
| 1                                                                 |      |
| aag gac cgc aag aag atc cag ttc tcg gtg ccc gcg ccc cct agc cag   | 524  |
| Lys Asp Arg Lys Lys Ile Gln Phe Ser Val Pro Ala Pro Pro Ser Gln   |      |
| 5 10 15                                                           |      |
| ctc gac ccc cgc cag gtg gag atg atc cgg cgc agg aga cca acg cct   | 572  |
| Leu Asp Pro Arg Gln Val Glu Met Ile Arg Arg Arg Pro Thr Pro       |      |
| 20 25 30 35                                                       |      |
| gcc atg ctg ttc cgg ctc tca gag cac tcc tca cca gag gag gaa gcc   | 620  |
| Ala Met Leu Phe Arg Leu Ser Glu His Ser Ser Pro Glu Glu Glu Ala   |      |
| 40 45 50                                                          |      |
| tcc ccc cac cag aga gcc tca gga gag ggg cac cat ctc aag tcg aag   | 668  |
| Ser Pro His Gln Arg Ala Ser Gly Glu Gly His His Leu Lys Ser Lys   |      |
| 55 60 65                                                          |      |
| aga ccc aac ccc tgt gcc tac aca cca cct tcg ctg aaa gct gtg cag   | 716  |
| Arg Pro Asn Pro Cys Ala Tyr Thr Pro Pro Ser Leu Lys Ala Val Gln   |      |
| 70 75 80                                                          |      |
| cgc att gct gag tct cac ctg cag tct atc agc aat ttg aat gag aac   | 764  |
| Arg Ile Ala Glu Ser His Leu Gln Ser Ile Ser Asn Leu Asn Glu Asn   |      |
| 85 90 95                                                          |      |
| cag gcc tca gag gag gag gat gag ctg ggg gag ctt cgg gag ctg ggt   | 812  |
| Gln Ala Ser Glu Glu Glu Asp Glu Leu Gly Glu Leu Arg Glu Leu Gly   |      |
| 100 105 110 115                                                   |      |
| tat cca aga gag gaa gat gag gag gaa gag gag gat gat gaa gaa gag   | 860  |
| Tyr Pro Arg Glu Glu Asp Glu Glu Glu Glu Glu Asp Asp Glu Glu Glu   |      |
| 120 125 130                                                       |      |
| gaa gaa gaa gag gac agc cag gct gaa gtc ctg aag gtc atc agg cag   | 908  |
| Glu Glu Glu Glu Asp Ser Gln Ala Glu Val Leu Lys Val Ile Arg Gln   |      |
| 135 140 145                                                       |      |
| tct gct ggg caa aag aca acc tgt ggc cag ggt ctg gaa ggg ccc tgg   | 956  |
| Ser Ala Gly Gln Lys Thr Thr Cys Gly Gln Gly Leu Glu Gly Pro Trp   |      |
| 150 155 160                                                       |      |
| gag cgc cca ccc cct ctg gat gag tcc gag aga gat gga ggc tct gag   | 1004 |
| Glu Arg Pro Pro Pro Leu Asp Glu Ser Glu Arg Asp Gly Gly Ser Glu   |      |
| 165 170 175                                                       |      |
| gac caa gtg gaa gac cca gca cta agt gag cct ggg gag gaa cct cag   | 1052 |
| Asp Gln Val Glu Asp Pro Ala Leu Ser Glu Pro Gly Glu Glu Pro Gln   |      |
| 180 185 190 195                                                   |      |
| cgc cct tcc ccc tct gag cct ggc aca tag gcacccagcc tgcattctcc     | 1102 |
| Arg Pro Ser Pro Ser Glu Pro Gly Thr *                             |      |
| 200                                                               |      |
| aggaggaagt ggaggggaca tcgctgttcc ccagaaaccc actctatcct caccctgttt | 1162 |
| tgtgtctcttc ccctgcctg ctagggtgc ggttctgac ttctagaaga ctaaggctgg   | 1222 |
| tctgtgtttg ctgttttgc cacccttggc tgataccag agaacctggg cacttgcgc    | 1282 |
| ctgatgcccc ccctgcag tcattctcc attcaccag cgggaggtgg gatgtgagac     | 1342 |
| agccacatt ggaaatcca gaaaaccggg aacagggatt tgcccttcac aattctactc   | 1402 |
| cccagatcct ctccctgga cacaggagac ccacaggga ggaccctaag atctggggaa   | 1462 |
| aggaggtcct gagaacctg aggtaccctt agatcctttt ctaccactt tcctatggag   | 1522 |

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gattccaagt caccacttct ctcaccggct tctaccaggg tccaggacta aggcgttttt 1582
ctccatagcc tcaacatttt gggaattctc ccttaatcac ccttgctcct cctgggtgcc 1642
tggaagatgg actggcagag acctctttgt tgcgttttgt gctttgatgc caggaatgcc 1702
gcctagttta tgtccccggt ggggcacaca gcggggggcg ccagggttttc cttgtccccc 1762
agctgctctg cccctttccc cttcttcctt gactccaggc ctgaaccctt cccgtgctgt 1822
aataaatctt tgtaaataa 1841

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```

<210> SEQ ID NO 76
<211> LENGTH: 204
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 76

```

```

Met Asp Pro Lys Asp Arg Lys Lys Ile Gln Phe Ser Val Pro Ala Pro
1           5           10          15
Pro Ser Gln Leu Asp Pro Arg Gln Val Glu Met Ile Arg Arg Arg Arg
                20          25          30
Pro Thr Pro Ala Met Leu Phe Arg Leu Ser Glu His Ser Ser Pro Glu
                35          40          45
Glu Glu Ala Ser Pro His Gln Arg Ala Ser Gly Glu Gly His His Leu
50          55          60
Lys Ser Lys Arg Pro Asn Pro Cys Ala Tyr Thr Pro Pro Ser Leu Lys
65          70          75          80
Ala Val Gln Arg Ile Ala Glu Ser His Leu Gln Ser Ile Ser Asn Leu
                85          90          95
Asn Glu Asn Gln Ala Ser Glu Glu Glu Asp Glu Leu Gly Glu Leu Arg
100         105         110
Glu Leu Gly Tyr Pro Arg Glu Glu Asp Glu Glu Glu Glu Asp Asp
115         120         125
Glu Glu Glu Glu Glu Glu Asp Ser Gln Ala Glu Val Leu Lys Val
130         135         140
Ile Arg Gln Ser Ala Gly Gln Lys Thr Thr Cys Gly Gln Gly Leu Glu
145         150         155         160
Gly Pro Trp Glu Arg Pro Pro Pro Leu Asp Glu Ser Glu Arg Asp Gly
165         170         175
Gly Ser Glu Asp Gln Val Glu Asp Pro Ala Leu Ser Glu Pro Gly Glu
180         185         190
Glu Pro Gln Arg Pro Ser Pro Ser Glu Pro Gly Thr
195         200

```

```

<210> SEQ ID NO 77
<211> LENGTH: 3745
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (124) ... (2220)

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<400> SEQUENCE: 77

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```

agcgggcgcct taaatagcat ccagagccgg cgcgggggcag ggagtgggct gcagtgcacag 60
ccggcgggcgg agcggccggt ccacggagga gaattcagct tagagaacta tcaacacagg 120
aca atg caa gcc cat gag ctg ttc cgg tat ttt cga atg cca gag ctg 168

```

| Met<br>1          | Gln               | Ala               | His               | Glu<br>5          | Leu               | Phe               | Arg               | Tyr               | Phe<br>10         | Arg               | Met               | Pro               | Glu<br>15         | Leu               |                   |      |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| ggt<br>Val        | gac<br>Asp        | ttc<br>Phe        | cga<br>Arg        | cag<br>Gln<br>20  | tac<br>Tyr        | gtg<br>Val        | cgt<br>Arg        | act<br>Thr<br>25  | ctt<br>Leu        | ccg<br>Pro        | acc<br>Thr        | aac<br>Asn        | acg<br>Thr        | ctt<br>Leu<br>30  | atg<br>Met        | 216  |
| ggc<br>Gly        | ttc<br>Phe        | gga<br>Gly        | gct<br>Ala<br>35  | ttt<br>Phe        | gca<br>Ala        | gca<br>Ala        | ctc<br>Leu        | acc<br>Thr<br>40  | acc<br>Thr        | ttc<br>Phe        | tgg<br>Trp        | tac<br>Tyr        | gcc<br>Ala<br>45  | acg<br>Thr        | aga<br>Arg        | 264  |
| ccc<br>Pro        | aaa<br>Lys        | ccc<br>Pro<br>50  | ctg<br>Leu        | aag<br>Lys        | ccg<br>Pro        | cca<br>Pro        | tgc<br>Cys<br>55  | gac<br>Asp        | ctc<br>Leu        | tcc<br>Ser        | atg<br>Met        | cag<br>Gln<br>60  | tca<br>Ser        | gtg<br>Val        | gaa<br>Glu        | 312  |
| gtg<br>Val        | gcg<br>Ala<br>65  | ggg<br>Gly        | agt<br>Ser        | ggg<br>Gly        | ggg<br>Gly        | gca<br>Ala<br>70  | cga<br>Arg        | aga<br>Arg        | tcc<br>Ser        | gca<br>Ala<br>75  | cta<br>Leu        | ctt<br>Leu        | gac<br>Asp        | agc<br>Ser        | gac<br>Asp        | 360  |
| gag<br>Glu<br>80  | ccc<br>Pro        | ttg<br>Leu        | gtg<br>Val        | tat<br>Tyr<br>85  | ttc<br>Phe        | tat<br>Tyr        | gat<br>Asp        | gat<br>Asp        | gtc<br>Val<br>90  | aca<br>Thr        | aca<br>Thr        | tta<br>Leu        | tac<br>Tyr        | gaa<br>Glu<br>95  | ggg<br>Gly        | 408  |
| ttc<br>Phe        | cag<br>Gln        | agg<br>Arg        | gga<br>Gly<br>100 | ata<br>Ile<br>100 | cag<br>Gln        | gtg<br>Val        | tca<br>Ser        | aat<br>Asn<br>105 | aat<br>Asn<br>105 | ggc<br>Gly        | cct<br>Pro        | tgt<br>Cys        | tta<br>Leu<br>110 | ggc<br>Gly<br>110 | tct<br>Ser        | 456  |
| cgg<br>Arg        | aaa<br>Lys        | cca<br>Pro<br>115 | gac<br>Asp        | caa<br>Gln        | ccc<br>Pro        | tat<br>Tyr        | gaa<br>Glu<br>120 | tgg<br>Trp<br>120 | ctt<br>Leu        | tca<br>Ser        | tat<br>Tyr        | aaa<br>Lys<br>125 | cag<br>Gln<br>125 | gtt<br>Val        | gca<br>Ala        | 504  |
| gaa<br>Glu        | ttg<br>Leu        | tcg<br>Ser<br>130 | gag<br>Glu        | tgc<br>Cys        | ata<br>Ile        | ggc<br>Gly<br>135 | tca<br>Ser        | gca<br>Ala<br>135 | ctg<br>Leu        | atc<br>Ile        | cag<br>Gln<br>140 | aag<br>Lys<br>140 | ggc<br>Gly<br>140 | ttc<br>Phe        | aag<br>Lys        | 552  |
| act<br>Thr        | gcc<br>Ala<br>145 | cca<br>Pro        | gat<br>Asp        | cag<br>Gln        | ttc<br>Phe        | att<br>Ile<br>150 | ggc<br>Gly        | atc<br>Ile        | ttt<br>Phe        | gct<br>Ala<br>155 | caa<br>Gln<br>155 | aat<br>Asn        | aga<br>Arg        | cct<br>Pro        | gag<br>Glu        | 600  |
| tgg<br>Trp<br>160 | gtg<br>Val        | att<br>Ile        | att<br>Ile        | gaa<br>Glu<br>165 | caa<br>Gln<br>165 | gga<br>Gly        | tgc<br>Cys        | ttt<br>Phe        | gct<br>Ala<br>170 | tat<br>Tyr<br>170 | tcg<br>Ser        | atg<br>Met        | gtg<br>Val        | atc<br>Ile<br>175 | gtt<br>Val<br>175 | 648  |
| cca<br>Pro        | ctt<br>Leu        | tat<br>Tyr        | gat<br>Asp<br>180 | acc<br>Thr<br>180 | ctt<br>Leu        | gga<br>Gly        | aat<br>Asn        | gaa<br>Glu<br>185 | gcc<br>Ala<br>185 | atc<br>Ile        | acg<br>Thr        | tac<br>Tyr        | ata<br>Ile<br>190 | gtc<br>Val<br>190 | aac<br>Asn        | 696  |
| aaa<br>Lys        | gct<br>Ala        | gaa<br>Glu<br>195 | ctc<br>Leu        | tct<br>Ser        | ctg<br>Leu        | gtt<br>Val        | ttt<br>Phe        | gtt<br>Val<br>200 | gac<br>Asp<br>200 | aag<br>Lys        | cca<br>Pro        | gag<br>Glu<br>205 | aag<br>Lys<br>205 | gcc<br>Ala<br>205 | aaa<br>Lys        | 744  |
| ctc<br>Leu        | tta<br>Leu<br>210 | tta<br>Leu        | gag<br>Glu        | ggg<br>Gly        | gta<br>Val        | gaa<br>Glu        | aat<br>Asn<br>215 | aag<br>Lys        | tta<br>Leu<br>215 | ata<br>Ile        | cca<br>Pro        | ggc<br>Gly<br>220 | ctt<br>Leu<br>220 | aaa<br>Lys        | atc<br>Ile        | 792  |
| ata<br>Ile<br>225 | gtt<br>Val        | gtc<br>Val        | atg<br>Met        | gat<br>Asp        | gcc<br>Ala        | tac<br>Tyr<br>230 | ggc<br>Gly        | agt<br>Ser        | gaa<br>Glu        | ctg<br>Leu        | gtg<br>Val<br>235 | gaa<br>Glu        | cga<br>Arg        | ggc<br>Gly        | cag<br>Gln        | 840  |
| agg<br>Arg<br>240 | tgt<br>Cys        | ggg<br>Gly        | gtg<br>Val        | gaa<br>Glu        | gtc<br>Val        | acc<br>Thr<br>245 | agc<br>Ser        | atg<br>Met        | aag<br>Lys        | gcg<br>Ala<br>250 | atg<br>Met        | gag<br>Glu        | gac<br>Asp        | ctg<br>Leu<br>255 | gga<br>Gly        | 888  |
| aga<br>Arg        | gcc<br>Ala        | aac<br>Asn        | aga<br>Arg        | cgg<br>Arg<br>260 | aag<br>Lys        | ccc<br>Pro        | aag<br>Lys        | cct<br>Pro        | cca<br>Pro<br>265 | gca<br>Ala        | cct<br>Pro        | gaa<br>Glu        | gat<br>Asp        | ctt<br>Leu<br>270 | gca<br>Ala        | 936  |
| gta<br>Val        | att<br>Ile        | tgt<br>Cys        | ttc<br>Phe<br>275 | aca<br>Thr        | agt<br>Ser        | gga<br>Gly        | act<br>Thr        | aca<br>Thr<br>280 | ggc<br>Gly        | aac<br>Asn        | ccc<br>Pro        | aaa<br>Lys        | gga<br>Gly<br>285 | gca<br>Ala        | atg<br>Met        | 984  |
| gtc<br>Val        | act<br>Thr        | cac<br>His        | cga<br>Arg        | aac<br>Asn<br>290 | ata<br>Ile        | gtg<br>Val        | agc<br>Ser        | gat<br>Asp<br>295 | tgt<br>Cys        | tca<br>Ser        | gct<br>Ala        | ttt<br>Phe<br>300 | gtg<br>Val        | aaa<br>Lys        | gca<br>Ala        | 1032 |
| aca               | gag               | aaa               | gca               | ctt               | ccc               | ttg               | agt               | gcc               | agt               | gac               | aca               | cac               | att               | tca               | tat               | 1080 |

-continued

|            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Thr<br>305 | Glu | Lys | Ala | Leu | Pro | Leu | Ser | Ala | Ser | Asp | Thr | His | Ile | Ser | Tyr |      |
| tta        | cca | ctt | gct | cac | att | tat | gaa | cag | tta | ttg | aag | tgt | gta | atg | ctg | 1128 |
| Leu        | Pro | Leu | Ala | His | Ile | Tyr | Glu | Gln | Leu | Leu | Lys | Cys | Val | Met | Leu |      |
| 320        |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |      |
| tgt        | cat | gga | gct | aaa | atc | gga | ttt | ttc | caa | gga | gat | atc | agg | ctg | ctc | 1176 |
| Cys        | His | Gly | Ala | Lys | Ile | Gly | Phe | Phe | Gln | Gly | Asp | Ile | Arg | Leu | Leu |      |
|            |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |      |
| atg        | gat | gac | ctc | aag | gtg | ctt | caa | ccc | act | gtc | ttc | ccc | gtg | gtt | cca | 1224 |
| Met        | Asp | Asp | Leu | Lys | Val | Leu | Gln | Pro | Thr | Val | Phe | Pro | Val | Val | Pro |      |
|            |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |      |
| aga        | ctg | ctg | aac | cgg | atg | ttt | gac | cga | att | ttc | gga | caa | gca | aac | acc | 1272 |
| Arg        | Leu | Leu | Asn | Arg | Met | Phe | Asp | Arg | Ile | Phe | Gly | Gln | Ala | Asn | Thr |      |
|            | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |      |
| acg        | ctg | aag | cga | tgg | ctc | ttg | gac | ttt | gcc | tcc | aag | agg | aaa | gaa | gca | 1320 |
| Thr        | Leu | Lys | Arg | Trp | Leu | Leu | Asp | Phe | Ala | Ser | Lys | Arg | Lys | Glu | Ala |      |
|            | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     |      |
| gag        | ctt | cgc | agc | ggc | atc | atc | aga | aac | aac | agc | ctg | tgg | gac | cgg | ctg | 1368 |
| Glu        | Leu | Arg | Ser | Gly | Ile | Ile | Arg | Asn | Asn | Ser | Leu | Trp | Asp | Arg | Leu |      |
| 400        |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |      |
| atc        | ttc | cac | aaa | gta | cag | tcg | agc | ctg | ggc | gga | aga | gtc | cgg | ctg | atg | 1416 |
| Ile        | Phe | His | Lys | Val | Gln | Ser | Ser | Leu | Gly | Gly | Arg | Val | Arg | Leu | Met |      |
|            |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |      |
| gtg        | aca | gga | gcc | gcc | ccg | gtg | tct | gcc | act | gtg | ctg | acg | ttc | ctc | aga | 1464 |
| Val        | Thr | Gly | Ala | Ala | Pro | Val | Ser | Ala | Thr | Val | Leu | Thr | Phe | Leu | Arg |      |
|            |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |      |
| gca        | gcc | ctg | ggc | tgt | cag | ttt | tat | gaa | gga | tac | gga | cag | aca | gag | tgc | 1512 |
| Ala        | Ala | Leu | Gly | Cys | Gln | Phe | Tyr | Glu | Gly | Tyr | Gly | Gln | Thr | Glu | Cys |      |
|            |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |      |
| act        | gcc | ggg | tgc | tgc | cta | acc | atg | cct | gga | gac | tgg | acc | gca | ggc | cat | 1560 |
| Thr        | Ala | Gly | Cys | Cys | Leu | Thr | Met | Pro | Gly | Asp | Trp | Thr | Ala | Gly | His |      |
|            | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     |      |
| gtt        | ggg | gcc | ccg | atg | ccg | tgc | aat | ttg | ata | aaa | ctt | gtt | gat | gtg | gaa | 1608 |
| Val        | Gly | Ala | Pro | Met | Pro | Cys | Asn | Leu | Ile | Lys | Leu | Val | Asp | Val | Glu |      |
| 480        |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |      |
| gaa        | atg | aat | tac | atg | gct | gcc | gag | ggc | gag | ggc | gag | gtg | tgt | gtg | aaa | 1656 |
| Glu        | Met | Asn | Tyr | Met | Ala | Ala | Glu | Gly | Glu | Gly | Glu | Val | Cys | Val | Lys |      |
|            |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |      |
| ggg        | cca | aat | gta | ttt | cag | ggc | tac | ttg | aag | gac | cca | gcg | aaa | aca | gca | 1704 |
| Gly        | Pro | Asn | Val | Phe | Gln | Gly | Tyr | Leu | Lys | Asp | Pro | Ala | Lys | Thr | Ala |      |
|            |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |      |
| gaa        | gct | ttg | gac | aaa | gac | ggc | tgg | tta | cac | aca | ggg | gac | att | gga | aaa | 1752 |
| Glu        | Ala | Leu | Asp | Lys | Asp | Gly | Trp | Leu | His | Thr | Gly | Asp | Ile | Gly | Lys |      |
|            |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |      |
| tgg        | tta | cca | aat | ggc | acc | ttg | aaa | att | atc | gac | cgg | aaa | aag | cac | ata | 1800 |
| Trp        | Leu | Pro | Asn | Gly | Thr | Leu | Lys | Ile | Ile | Asp | Arg | Lys | Lys | His | Ile |      |
|            | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     |      |
| ttt        | aag | ctg | gca | caa | gga | gaa | tac | ata | gcc | cct | gaa | aag | att | gaa | aat | 1848 |
| Phe        | Lys | Leu | Ala | Gln | Gly | Glu | Tyr | Ile | Ala | Pro | Glu | Lys | Ile | Glu | Asn |      |
| 560        |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |      |
| atc        | tac | atg | cga | agt | gag | cct | gtt | gct | cag | gtg | ttt | gtc | cac | gga | gaa | 1896 |
| Ile        | Tyr | Met | Arg | Ser | Glu | Pro | Val |     | Gln | Val | Phe | Val | His | Gly | Glu |      |
|            |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |      |
| agc        | ctg | cag | gca | ttt | ctc | att | gca | att | gtg | gta | cca | gat | gtt | gag | aca | 1944 |
| Ser        | Leu | Gln | Ala | Phe | Leu | Ile | Ala | Ile | Val | Val | Pro | Asp | Val | Glu | Thr |      |
|            |     |     | 595 |     |     |     | 600 |     |     |     |     |     |     | 605 |     |      |
| tta        | tgt | tcc | tgg | gcc | caa | aag | aga | gga | ttt | gaa | ggg | tcg | ttt | gag | gaa | 1992 |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| Leu Cys Ser Trp Ala Gln Lys Arg Gly Phe Glu Gly Ser Phe Glu Glu    |      |
| 610 615 620                                                        |      |
| ctg tgc aga aat aag gat gtc aaa aaa gct atc ctc gaa gat atg gtg    | 2040 |
| Leu Cys Arg Asn Lys Asp Val Lys Lys Ala Ile Leu Glu Asp Met Val    |      |
| 625 630 635                                                        |      |
| aga ctt ggg aag gat tct ggt ctg aaa cca ttt gaa cag gtc aaa ggc    | 2088 |
| Arg Leu Gly Lys Asp Ser Gly Leu Lys Pro Phe Glu Gln Val Lys Gly    |      |
| 640 645 650 655                                                    |      |
| atc aca ttg cac cct gaa tta ttt tct atc gac aat ggc ctt ctg act    | 2136 |
| Ile Thr Leu His Pro Glu Leu Phe Ser Ile Asp Asn Gly Leu Leu Thr    |      |
| 660 665 670                                                        |      |
| cca aca atg aag gcg aaa agg cca gag ctg cgg aac tat ttc agg tcg    | 2184 |
| Pro Thr Met Lys Ala Lys Arg Pro Glu Leu Arg Asn Tyr Phe Arg Ser    |      |
| 675 680 685                                                        |      |
| cag ata gat gac ctc tat tcc act atc aag gtt tag tgtgaagaag         | 2230 |
| Gln Ile Asp Asp Leu Tyr Ser Thr Ile Lys Val *                      |      |
| 690 695                                                            |      |
| aaagctcaga ggaaatggca cagttccaca atctcttctc ctgctgatgg ccttcatgtt  | 2290 |
| gttaattttt aatacagcaa gtgtagggaa ggaagcgttc gtgtttgact tgtccattcg  | 2350 |
| gggttcttct cataggaatg ctagaggaaa cagaacaccg ccttacagtc acctcatgtt  | 2410 |
| gcagaccatg tttatggtaa tacacacttt ccaaaatgag ccttaaaaat tgtaaagggg  | 2470 |
| atactataaa tgtgctaagt tatttgagac ttctctcagtt taaaaagtgg gttttaaatc | 2530 |
| ttctgtctcc ctgcttttct aatcaagggg ttaggacttt gctatctctg agatgtctgc  | 2590 |
| tacttgctgc aaattctgca gctgtctgct gctctaaaga gtacagtgc ctagagggaa   | 2650 |
| gtgttccctt taaaaataag aacaactgtc ctggctggag aatctcaca gcggaccaga   | 2710 |
| gatcttttta aatccctgct actgtccctt ctcacaggca ttcacagaac ccttctgatt  | 2770 |
| cgtaaggggt acgaaactca tgttcttctc cagtccctg tggtttctgt tggagcataa   | 2830 |
| ggtttccagt aagcgggagg gcagatccaa ctcagaacca tgcagataag gagcctctgg  | 2890 |
| caaatgggtg ctcacagaa cgcgtaggatt ctctttcatg gcagaatgct cttggactcg  | 2950 |
| gttctccagg cctgattccc cgactccatc ctttttcagg ggttatttaa aaatctgcct  | 3010 |
| tagattctat agtgaagaca agcattttcaa gaaagagtta cctggatcag ccatgctcag | 3070 |
| ctgtgacgcc tgaataactg tctactttat cttcactgaa cactcactc tgtgtaaagg   | 3130 |
| ccaacagatt tttaatgtgg ttttcatatc aaaagatcat gttgggatta acttgccttt  | 3190 |
| ttccccaaaa aataaactct caggcaagca tttcttttaa gctattaagg gagtatatac  | 3250 |
| ttgagtactt attgaaatgg acagtaataa gcaaatgttc ttataatgct acctgatttc  | 3310 |
| tatgaaatgt gtttgacaag ccaaaattct aggatgtaga aatctggaaa gttcatttcc  | 3370 |
| tgggattcac ttctccaggg atttttttaa gtttaatttg gaaattaaca gcagttcact  | 3430 |
| ttattgtgag tctttgccac atttgactga attgagctgt catttgtaca tttaaagcag  | 3490 |
| ctgttttggg gtctgtgaga gtacatgtat tatatacaag cacaacaggg cttgcactaa  | 3550 |
| agaattgtca ttgtaataac actacttggt agcctaact catatatgta ttcttaattg   | 3610 |
| cacaaaaagt caataatttg tcacctggg gttttgaatg tttgctttaa gtgttggtca   | 3670 |
| ttctatgtt ttataaacca aaacaaaatt tccaaaaaca atgaaggaaa ccaaaataaa   | 3730 |
| tatttctgca tttcg                                                   | 3745 |

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<210> SEQ ID NO 78  
 <211> LENGTH: 698  
 <212> TYPE: PRT  
 <213> ORGANISM: human

<400> SEQUENCE: 78

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Met Gln Ala His Glu Leu Phe Arg Tyr Phe Arg Met Pro Glu Leu Val
1          5          10          15

Asp Phe Arg Gln Tyr Val Arg Thr Leu Pro Thr Asn Thr Leu Met Gly
20        25        30

Phe Gly Ala Phe Ala Ala Leu Thr Phe Trp Tyr Ala Thr Arg Pro
35        40        45

Lys Pro Leu Lys Pro Pro Cys Asp Leu Ser Met Gln Ser Val Glu Val
50        55        60

Ala Gly Ser Gly Gly Ala Arg Arg Ser Ala Leu Leu Asp Ser Asp Glu
65        70        75        80

Pro Leu Val Tyr Phe Tyr Asp Asp Val Thr Thr Leu Tyr Glu Gly Phe
85        90        95

Gln Arg Gly Ile Gln Val Ser Asn Asn Gly Pro Cys Leu Gly Ser Arg
100       105       110

Lys Pro Asp Gln Pro Tyr Glu Trp Leu Ser Tyr Lys Gln Val Ala Glu
115       120       125

Leu Ser Glu Cys Ile Gly Ser Ala Leu Ile Gln Lys Gly Phe Lys Thr
130       135       140

Ala Pro Asp Gln Phe Ile Gly Ile Phe Ala Gln Asn Arg Pro Glu Trp
145       150       155       160

Val Ile Ile Glu Gln Gly Cys Phe Ala Tyr Ser Met Val Ile Val Pro
165       170       175

Leu Tyr Asp Thr Leu Gly Asn Glu Ala Ile Thr Tyr Ile Val Asn Lys
180       185       190

Ala Glu Leu Ser Leu Val Phe Val Asp Lys Pro Glu Lys Ala Lys Leu
195       200       205

Leu Leu Glu Gly Val Glu Asn Lys Leu Ile Pro Gly Leu Lys Ile Ile
210       215       220

Val Val Met Asp Ala Tyr Gly Ser Glu Leu Val Glu Arg Gly Gln Arg
225       230       235       240

Cys Gly Val Glu Val Thr Ser Met Lys Ala Met Glu Asp Leu Gly Arg
245       250       255

Ala Asn Arg Arg Lys Pro Lys Pro Pro Ala Pro Glu Asp Leu Ala Val
260       265       270

Ile Cys Phe Thr Ser Gly Thr Thr Gly Asn Pro Lys Gly Ala Met Val
275       280       285

Thr His Arg Asn Ile Val Ser Asp Cys Ser Ala Phe Val Lys Ala Thr
290       295       300

Glu Lys Ala Leu Pro Leu Ser Ala Ser Asp Thr His Ile Ser Tyr Leu
305       310       315       320

Pro Leu Ala His Ile Tyr Glu Gln Leu Leu Lys Cys Val Met Leu Cys
325       330       335

His Gly Ala Lys Ile Gly Phe Phe Gln Gly Asp Ile Arg Leu Leu Met
340       345       350

Asp Asp Leu Lys Val Leu Gln Pro Thr Val Phe Pro Val Val Pro Arg
355       360       365

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Asn | Arg | Met | Phe | Asp | Arg | Ile | Phe | Gly | Gln | Ala | Asn | Thr | Thr |
| 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Leu | Lys | Arg | Trp | Leu | Leu | Asp | Phe | Ala | Ser | Lys | Arg | Lys | Glu | Ala | Glu |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Leu | Arg | Ser | Gly | Ile | Ile | Arg | Asn | Asn | Ser | Leu | Trp | Asp | Arg | Leu | Ile |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Phe | His | Lys | Val | Gln | Ser | Ser | Leu | Gly | Gly | Arg | Val | Arg | Leu | Met | Val |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Thr | Gly | Ala | Ala | Pro | Val | Ser | Ala | Thr | Val | Leu | Thr | Phe | Leu | Arg | Ala |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Ala | Leu | Gly | Cys | Gln | Phe | Tyr | Glu | Gly | Tyr | Gly | Gln | Thr | Glu | Cys | Thr |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Gly | Cys | Cys | Leu | Thr | Met | Pro | Gly | Asp | Trp | Thr | Ala | Gly | His | Val |
| 465 |     |     |     |     | 470 |     |     |     | 475 |     |     |     |     |     | 480 |
| Gly | Ala | Pro | Met | Pro | Cys | Asn | Leu | Ile | Lys | Leu | Val | Asp | Val | Glu | Glu |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Met | Asn | Tyr | Met | Ala | Ala | Glu | Gly | Glu | Gly | Glu | Val | Cys | Val | Lys | Gly |
|     |     | 500 |     |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Pro | Asn | Val | Phe | Gln | Gly | Tyr | Leu | Lys | Asp | Pro | Ala | Lys | Thr | Ala | Glu |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Ala | Leu | Asp | Lys | Asp | Gly | Trp | Leu | His | Thr | Gly | Asp | Ile | Gly | Lys | Trp |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Leu | Pro | Asn | Gly | Thr | Leu | Lys | Ile | Ile | Asp | Arg | Lys | Lys | His | Ile | Phe |
| 545 |     |     |     |     | 550 |     |     |     | 555 |     |     |     |     |     | 560 |
| Lys | Leu | Ala | Gln | Gly | Glu | Tyr | Ile | Ala | Pro | Glu | Lys | Ile | Glu | Asn | Ile |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Tyr | Met | Arg | Ser | Glu | Pro | Val | Ala | Gln | Val | Phe | Val | His | Gly | Glu | Ser |
|     |     | 580 |     |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Leu | Gln | Ala | Phe | Leu | Ile | Ala | Ile | Val | Val | Pro | Asp | Val | Glu | Thr | Leu |
|     | 595 |     |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Cys | Ser | Trp | Ala | Gln | Lys | Arg | Gly | Phe | Glu | Gly | Ser | Phe | Glu | Glu | Leu |
|     | 610 |     |     |     | 615 |     |     |     |     |     | 620 |     |     |     |     |
| Cys | Arg | Asn | Lys | Asp | Val | Lys | Lys | Ala | Ile | Leu | Glu | Asp | Met | Val | Arg |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Leu | Gly | Lys | Asp | Ser | Gly | Leu | Lys | Pro | Phe | Glu | Gln | Val | Lys | Gly | Ile |
|     |     |     | 645 |     |     |     |     | 650 |     |     |     |     |     | 655 |     |
| Thr | Leu | His | Pro | Glu | Leu | Phe | Ser | Ile | Asp | Asn | Gly | Leu | Leu | Thr | Pro |
|     |     | 660 |     |     |     |     |     | 665 |     |     |     |     | 670 |     |     |
| Thr | Met | Lys | Ala | Lys | Arg | Pro | Glu | Leu | Arg | Asn | Tyr | Phe | Arg | Ser | Gln |
|     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| Ile | Asp | Asp | Leu | Tyr | Ser | Thr | Ile | Lys | Val |     |     |     |     |     |     |
|     | 690 |     |     |     |     | 695 |     |     |     |     |     |     |     |     |     |

<210> SEQ ID NO 79  
 <211> LENGTH: 3809  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (188) ... (2284)

<400> SEQUENCE: 79

agcggatcgt ggctcagccg cggcgggtggc gggggcgcaa ccagcgggccc gaggcggcgg

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| cgccagcggc gccttaata gcatccagag ccggcgcggg gcaggagtg ggtgcagtg                                                                                        | 120  |
| acagccggcg gcggagcggc cgggtccacgg aggagaattc agcttagaga actatcaaca                                                                                    | 180  |
| caggaca atg caa gcc cat gag ctg ttc cgg tat ttt cga atg cca gag<br>Met Gln Ala His Glu Leu Phe Arg Tyr Phe Arg Met Pro Glu<br>1 5 10                  | 229  |
| ctg gtt gac ttc cga cag tac gtg cgt act ctt ccg acc aac acg ctt<br>Leu Val Asp Phe Arg Gln Tyr Val Arg Thr Leu Pro Thr Asn Thr Leu<br>15 20 25 30     | 277  |
| atg ggc ttc gga gct ttt gca gca ctc acc acc ttc tgg tac gcc acg<br>Met Gly Phe Gly Ala Phe Ala Ala Leu Thr Thr Phe Trp Tyr Ala Thr<br>35 40 45        | 325  |
| aga ccc aaa ccc ctg aag ccg cca tgc gac ctc tcc atg cag tca gtg<br>Arg Pro Lys Pro Leu Lys Pro Pro Cys Asp Leu Ser Met Gln Ser Val<br>50 55 60        | 373  |
| gaa gtg gcg ggt agt ggt ggt gca cga aga tcc gca cta ctt gac agc<br>Glu Val Ala Gly Ser Gly Gly Ala Arg Arg Ser Ala Leu Leu Asp Ser<br>65 70 75        | 421  |
| gac gag ccc ttg gtg tat ttc tat gat gat gtc aca aca tta tac gaa<br>Asp Glu Pro Leu Val Tyr Phe Tyr Asp Asp Val Thr Thr Leu Tyr Glu<br>80 85 90        | 469  |
| ggt ttc cag agg gga ata cag gtg tca aat aat ggc cct tgt tta ggc<br>Gly Phe Gln Arg Gly Ile Gln Val Ser Asn Asn Gly Pro Cys Leu Gly<br>95 100 105 110  | 517  |
| tct cgg aaa cca gac caa ccc tat gaa tgg ctt tca tat aaa cag gtt<br>Ser Arg Lys Pro Asp Gln Pro Tyr Glu Trp Leu Ser Tyr Lys Gln Val<br>115 120 125     | 565  |
| gca gaa ttg tcg gag tgc ata ggc tca gca ctg atc cag aag ggc ttc<br>Ala Glu Leu Ser Glu Cys Ile Gly Ser Ala Leu Ile Gln Lys Gly Phe<br>130 135 140     | 613  |
| aag act gcc cca gat cag ttc att ggc atc ttt gct caa aat aga cct<br>Lys Thr Ala Pro Asp Gln Phe Ile Gly Ile Phe Ala Gln Asn Arg Pro<br>145 150 155     | 661  |
| gag tgg gtg att att gaa caa gga tgc ttt gct tat tcg atg gtg atc<br>Glu Trp Val Ile Ile Glu Gln Gly Cys Phe Ala Tyr Ser Met Val Ile<br>160 165 170     | 709  |
| gtt cca ctt tat gat acc ctt gga aat gaa gcc atc acg tac ata gtc<br>Val Pro Leu Tyr Asp Thr Leu Gly Asn Glu Ala Ile Thr Tyr Ile Val<br>175 180 185 190 | 757  |
| aac aaa gct gaa ctc tct ctg gtt ttt gtt gac aag cca gag aag gcc<br>Asn Lys Ala Glu Leu Ser Leu Val Phe Val Asp Lys Pro Glu Lys Ala<br>195 200 205     | 805  |
| aaa ctc tta tta gag ggt gta gaa aat aag tta ata cca ggc ctt aaa<br>Lys Leu Leu Leu Glu Gly Val Glu Asn Lys Leu Ile Pro Gly Leu Lys<br>210 215 220     | 853  |
| atc ata gtt gtc atg gat gcc tac ggc agt gaa ctg gtg gaa cga ggc<br>Ile Ile Val Val Met Asp Ala Tyr Gly Ser Glu Leu Val Glu Arg Gly<br>225 230 235     | 901  |
| cag agg tgt ggg gtg gaa gtc acc agc atg aag gcg atg gag gac ctg<br>Gln Arg Cys Gly Val Glu Val Thr Ser Met Lys Ala Met Glu Asp Leu<br>240 245 250     | 949  |
| gga aga gcc aac aga cgg aag ccc aag cct cca gca cct gaa gat ctt<br>Gly Arg Ala Asn Arg Arg Lys Pro Lys Pro Pro Ala Pro Glu Asp Leu<br>255 260 265 270 | 997  |
| gca gta att tgt ttc aca agt gga act aca ggc aac ccc aaa gga gca<br>Ala Val Ile Cys Phe Thr Ser Gly Thr Thr Gly Asn Pro Lys Gly Ala<br>275 280 285     | 1045 |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| atg gtc act cac cga aac ata gtg agc gat tgt tca gct ttt gtg aaa | 1093 |
| Met Val Thr His Arg Asn Ile Val Ser Asp Cys Ser Ala Phe Val Lys |      |
| 290 295 300                                                     |      |
| gca aca gag aat aca gtc aat cct tgc cca gat gat act ttg ata tct | 1141 |
| Ala Thr Glu Asn Thr Val Asn Pro Cys Pro Asp Asp Thr Leu Ile Ser |      |
| 305 310 315                                                     |      |
| ttc ttg cct ctc gcc cat atg ttt gag aga gtt gta gag tgt gta atg | 1189 |
| Phe Leu Pro Leu Ala His Met Phe Glu Arg Val Val Glu Cys Val Met |      |
| 320 325 330                                                     |      |
| ctg tgt cat gga gct aaa atc gga ttt ttc caa gga gat atc agg ctg | 1237 |
| Leu Cys His Gly Ala Lys Ile Gly Phe Phe Gln Gly Asp Ile Arg Leu |      |
| 335 340 345 350                                                 |      |
| ctc atg gat gac ctc aag gtg ctt caa ccc act gtc ttc ccc gtg gtt | 1285 |
| Leu Met Asp Asp Leu Lys Val Leu Gln Pro Thr Val Phe Pro Val Val |      |
| 355 360 365                                                     |      |
| cca aga ctg ctg aac cgg atg ttt gac cga att ttc gga caa gca aac | 1333 |
| Pro Arg Leu Leu Asn Arg Met Phe Asp Arg Ile Phe Gly Gln Ala Asn |      |
| 370 375 380                                                     |      |
| acc acg ctg aag cga tgg ctc ttg gac ttt gcc tcc aag agg aaa gaa | 1381 |
| Thr Thr Leu Lys Arg Trp Leu Leu Asp Phe Ala Ser Lys Arg Lys Glu |      |
| 385 390 395                                                     |      |
| gca gag ctt cgc agc ggc atc atc aga aac aac agc ctg tgg gac cgg | 1429 |
| Ala Glu Leu Arg Ser Gly Ile Ile Arg Asn Asn Ser Leu Trp Asp Arg |      |
| 400 405 410                                                     |      |
| ctg atc ttc cac aaa gta cag tcg agc ctg ggc gga aga gtc cgg ctg | 1477 |
| Leu Ile Phe His Lys Val Gln Ser Ser Leu Gly Gly Arg Val Arg Leu |      |
| 415 420 425 430                                                 |      |
| atg gtg aca gga gcc gcc ccg gtg tct gcc act gtg ctg acg ttc ctc | 1525 |
| Met Val Thr Gly Ala Ala Pro Val Ser Ala Thr Val Leu Thr Phe Leu |      |
| 435 440 445                                                     |      |
| aga gca gcc ctg ggc tgt cag ttt tat gaa gga tac gga cag aca gag | 1573 |
| Arg Ala Ala Leu Gly Cys Gln Phe Tyr Glu Gly Tyr Gly Gln Thr Glu |      |
| 450 455 460                                                     |      |
| tgc act gcc ggg tgc tgc cta acc atg cct gga gac tgg acc gca ggc | 1621 |
| Cys Thr Ala Gly Cys Cys Leu Thr Met Pro Gly Asp Trp Thr Ala Gly |      |
| 465 470 475                                                     |      |
| cat gtt ggg gcc ccg atg ccg tgc aat ttg ata aaa ctt gtt gat gtg | 1669 |
| His Val Gly Ala Pro Met Pro Cys Asn Leu Ile Lys Leu Val Asp Val |      |
| 480 485 490                                                     |      |
| gaa gaa atg aat tac atg gct gcc gag ggc gag ggc gag gtg tgt gtg | 1717 |
| Glu Glu Met Asn Tyr Met Ala Ala Glu Gly Glu Gly Glu Val Cys Val |      |
| 495 500 505 510                                                 |      |
| aaa ggg cca aat gta ttt cag ggc tac ttg aag gac cca gcg aaa aca | 1765 |
| Lys Gly Pro Asn Val Phe Gln Gly Tyr Leu Lys Asp Pro Ala Lys Thr |      |
| 515 520 525                                                     |      |
| gca gaa gct ttg gac aaa gac ggc tgg tta cac aca ggg gac att gga | 1813 |
| Ala Glu Ala Leu Asp Lys Asp Gly Trp Leu His Thr Gly Asp Ile Gly |      |
| 530 535 540                                                     |      |
| aaa tgg tta cca aat ggc acc ttg aaa att atc gac cgg aaa aag cac | 1861 |
| Lys Trp Leu Pro Asn Gly Thr Leu Lys Ile Ile Asp Arg Lys Lys His |      |
| 545 550 555                                                     |      |
| ata ttt aag ctg gca caa gga gaa tac ata gcc cct gaa aag att gaa | 1909 |
| Ile Phe Lys Leu Ala Gln Gly Glu Tyr Ile Ala Pro Glu Lys Ile Glu |      |
| 560 565 570                                                     |      |
| aat atc tac atg cga agt gag cct gtt gct cag gtg ttt gtc cac gga | 1957 |
| Asn Ile Tyr Met Arg Ser Glu Pro Val Ala Gln Val Phe Val His Gly |      |
| 575 580 585 590                                                 |      |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| gaa agc ctg cag gca ttt ctc att gca att gtg gta cca gat gtt gag    | 2005 |
| Glu Ser Leu Gln Ala Phe Leu Ile Ala Ile Val Val Pro Asp Val Glu    |      |
| 595 600 605                                                        |      |
| aca tta tgt tcc tgg gcc caa aag aga gga ttt gaa ggg tcg ttt gag    | 2053 |
| Thr Leu Cys Ser Trp Ala Gln Lys Arg Gly Phe Glu Gly Ser Phe Glu    |      |
| 610 615 620                                                        |      |
| gaa ctg tgc aga aat aag gat gtc aaa aaa gct atc ctc gaa gat atg    | 2101 |
| Glu Leu Cys Arg Asn Lys Asp Val Lys Lys Ala Ile Leu Glu Asp Met    |      |
| 625 630 635                                                        |      |
| gtg aga ctt ggg aag gat tct ggt ctg aaa cca ttt gaa cag gtc aaa    | 2149 |
| Val Arg Leu Gly Lys Asp Ser Gly Leu Lys Pro Phe Glu Gln Val Lys    |      |
| 640 645 650                                                        |      |
| ggc atc aca ttg cac cct gaa tta ttt tct atc gac aat ggc ctt ctg    | 2197 |
| Gly Ile Thr Leu His Pro Glu Leu Phe Ser Ile Asp Asn Gly Leu Leu    |      |
| 655 660 665 670                                                    |      |
| act cca aca atg aag gcg aaa agg cca gag ctg cgg aac tat ttc agg    | 2245 |
| Thr Pro Thr Met Lys Ala Lys Arg Pro Glu Leu Arg Asn Tyr Phe Arg    |      |
| 675 680 685                                                        |      |
| tcg cag ata gat gac ctc tat tcc act atc aag gtt tag tgtgaagaag     | 2294 |
| Ser Gln Ile Asp Asp Leu Tyr Ser Thr Ile Lys Val *                  |      |
| 690 695                                                            |      |
| aaagctcaga ggaaatggca cagttccaca atctcttctc ctgctgatgg ccttcattgtt | 2354 |
| gttaattttg aatacagcaa gtgtagggaa ggaagcgctc gtgtttgact tgtccattcg  | 2414 |
| gggttcttct cataggaatg ctagaggaaa cagaacaccg ccttacagtc acctcatgtt  | 2474 |
| gcagaccatg tttatggtaa tacacacttt ccaaaatgag ccttaaaaat tgtaaagggg  | 2534 |
| atactataaa tgtgctaagt tatttgagac ttcctcagtt taaaaagtgg gttttaaatc  | 2594 |
| ttctgtctcc ctgcttttct aatcaagggg ttaggacttt gctatctctg agatgtctgc  | 2654 |
| tacttgctgc aaattctgca gctgtctgct gctctaaaga gtacagtgc ctgaggggaa   | 2714 |
| gtgttccctt taaaaataag aacaactgtc ctggctggag aatctcacia gcggaccaga  | 2774 |
| gatcttttta aatccctgct actgtccctt ctcacaggca ttcacagaac ccttctgatt  | 2834 |
| cgttaagggtt acgaaactca tgttcttctc cagtccctcg tggtttctgt tggagcataa | 2894 |
| ggtttccagt aagcgggagg gcagatccaa ctcagaacca tgcagataag gagectctgg  | 2954 |
| caaatgggtg ctcactcagaa cgcgtggatt ctctttcatg gcagaatgct cttggactcg | 3014 |
| gttctccagg cctgattccc cgactccatc ctttttcagg ggttatttaa aaatctgcct  | 3074 |
| tagattctat agtgaagaca agcatttcaa gaaagagtta cctggatcag ccatgctcag  | 3134 |
| ctgtgacgcc tgaataactg tctactttat cttactgaa cactcactc tgtgtaaagg    | 3194 |
| ccaacagatt ttaatgtgg ttttcatatc aaaagatcat gttgggatta acttgccttt   | 3254 |
| ttccccaaaa aataaactct caggcaagca tttctttaaa gctattaagg gagtatatac  | 3314 |
| ttgagtactt attgaaatgg acagtaataa gcaaatgttc ttataatgct acctgatttc  | 3374 |
| tatgaaatgt gtttgacaag ccaaaattct aggatgtaga aatctggaaa gttcatttcc  | 3434 |
| tgggattcac ttctccaggg attttttaaa gttaatttgg gaaattaaca gcagttcact  | 3494 |
| ttattgtgag tctttgccac atttgactga attgagctgt catttgtaca tttaaagcag  | 3554 |
| ctgttttggg gtctgtgaga gtacatgtat tatatacaag cacaacaggg cttgcactaa  | 3614 |
| agaattgtca ttgtaataac actacttggt agcctaactt catatatgta ttcttaattg  | 3674 |
| cacaaaaagt caataatttg tcaccttggg gttttgaatg tttgctttaa gtgttggcta  | 3734 |

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tttctatgtt ttataaacca aaacaaaatt tccaaaaaca atgaaggaaa ccaaaataaa 3794

tattttctgca tttcgc 3809

&lt;210&gt; SEQ ID NO 80

&lt;211&gt; LENGTH: 698

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 80

Met Gln Ala His Glu Leu Phe Arg Tyr Phe Arg Met Pro Glu Leu Val  
1 5 10 15

Asp Phe Arg Gln Tyr Val Arg Thr Leu Pro Thr Asn Thr Leu Met Gly  
20 25 30

Phe Gly Ala Phe Ala Ala Leu Thr Thr Phe Trp Tyr Ala Thr Arg Pro  
35 40 45

Lys Pro Leu Lys Pro Pro Cys Asp Leu Ser Met Gln Ser Val Glu Val  
50 55 60

Ala Gly Ser Gly Gly Ala Arg Arg Ser Ala Leu Leu Asp Ser Asp Glu  
65 70 75 80

Pro Leu Val Tyr Phe Tyr Asp Asp Val Thr Thr Leu Tyr Glu Gly Phe  
85 90 95

Gln Arg Gly Ile Gln Val Ser Asn Asn Gly Pro Cys Leu Gly Ser Arg  
100 105 110

Lys Pro Asp Gln Pro Tyr Glu Trp Leu Ser Tyr Lys Gln Val Ala Glu  
115 120 125

Leu Ser Glu Cys Ile Gly Ser Ala Leu Ile Gln Lys Gly Phe Lys Thr  
130 135 140

Ala Pro Asp Gln Phe Ile Gly Ile Phe Ala Gln Asn Arg Pro Glu Trp  
145 150 155 160

Val Ile Ile Glu Gln Gly Cys Phe Ala Tyr Ser Met Val Ile Val Pro  
165 170 175

Leu Tyr Asp Thr Leu Gly Asn Glu Ala Ile Thr Tyr Ile Val Asn Lys  
180 185 190

Ala Glu Leu Ser Leu Val Phe Val Asp Lys Pro Glu Lys Ala Lys Leu  
195 200 205

Leu Leu Glu Gly Val Glu Asn Lys Leu Ile Pro Gly Leu Lys Ile Ile  
210 215 220

Val Val Met Asp Ala Tyr Gly Ser Glu Leu Val Glu Arg Gly Gln Arg  
225 230 235 240

Cys Gly Val Glu Val Thr Ser Met Lys Ala Met Glu Asp Leu Gly Arg  
245 250 255

Ala Asn Arg Arg Lys Pro Lys Pro Pro Ala Pro Glu Asp Leu Ala Val  
260 265 270

Ile Cys Phe Thr Ser Gly Thr Thr Gly Asn Pro Lys Gly Ala Met Val  
275 280 285

Thr His Arg Asn Ile Val Ser Asp Cys Ser Ala Phe Val Lys Ala Thr  
290 295 300

Glu Asn Thr Val Asn Pro Cys Pro Asp Asp Thr Leu Ile Ser Phe Leu  
305 310 315 320

Pro Leu Ala His Met Phe Glu Arg Val Val Glu Cys Val Met Leu Cys  
325 330 335

His Gly Ala Lys Ile Gly Phe Phe Gln Gly Asp Ile Arg Leu Leu Met

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| 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Asp | Leu | Lys | Val | Leu | Gln | Pro | Thr | Val | Phe | Pro | Val | Val | Pro | Arg |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Leu | Leu | Asn | Arg | Met | Phe | Asp | Arg | Ile | Phe | Gly | Gln | Ala | Asn | Thr | Thr |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Leu | Lys | Arg | Trp | Leu | Leu | Asp | Phe | Ala | Ser | Lys | Arg | Lys | Glu | Ala | Glu |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Leu | Arg | Ser | Gly | Ile | Ile | Arg | Asn | Asn | Ser | Leu | Trp | Asp | Arg | Leu | Ile |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Phe | His | Lys | Val | Gln | Ser | Ser | Leu | Gly | Gly | Arg | Val | Arg | Leu | Met | Val |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Thr | Gly | Ala | Ala | Pro | Val | Ser | Ala | Thr | Val | Leu | Thr | Phe | Leu | Arg | Ala |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Ala | Leu | Gly | Cys | Gln | Phe | Tyr | Glu | Gly | Tyr | Gly | Gln | Thr | Glu | Cys | Thr |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ala | Gly | Cys | Cys | Leu | Thr | Met | Pro | Gly | Asp | Trp | Thr | Ala | Gly | His | Val |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Gly | Ala | Pro | Met | Pro | Cys | Asn | Leu | Ile | Lys | Leu | Val | Asp | Val | Glu | Glu |
|     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Met | Asn | Tyr | Met | Ala | Ala | Glu | Gly | Glu | Gly | Glu | Val | Cys | Val | Lys | Gly |
|     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |     |
| Pro | Asn | Val | Phe | Gln | Gly | Tyr | Leu | Lys | Asp | Pro | Ala | Lys | Thr | Ala | Glu |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Ala | Leu | Asp | Lys | Asp | Gly | Trp | Leu | His | Thr | Gly | Asp | Ile | Gly | Lys | Trp |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Leu | Pro | Asn | Gly | Thr | Leu | Lys | Ile | Ile | Asp | Arg | Lys | Lys | His | Ile | Phe |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Lys | Leu | Ala | Gln | Gly | Glu | Tyr | Ile | Ala | Pro | Glu | Lys | Ile | Glu | Asn | Ile |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Tyr | Met | Arg | Ser | Glu | Pro | Val | Ala | Gln | Val | Phe | Val | His | Gly | Glu | Ser |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Leu | Gln | Ala | Phe | Leu | Ile | Ala | Ile | Val | Val | Pro | Asp | Val | Glu | Thr | Leu |
|     | 595 |     |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Cys | Ser | Trp | Ala | Gln | Lys | Arg | Gly | Phe | Glu | Gly | Ser | Phe | Glu | Glu | Leu |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| Cys | Arg | Asn | Lys | Asp | Val | Lys | Lys | Ala | Ile | Leu | Glu | Asp | Met | Val | Arg |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Leu | Gly | Lys | Asp | Ser | Gly | Leu | Lys | Pro | Phe | Glu | Gln | Val | Lys | Gly | Ile |
|     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     | 655 |     |
| Thr | Leu | His | Pro | Glu | Leu | Phe | Ser | Ile | Asp | Asn | Gly | Leu | Leu | Thr | Pro |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     | 670 |     |     |     |
| Thr | Met | Lys | Ala | Lys | Arg | Pro | Glu | Leu | Arg | Asn | Tyr | Phe | Arg | Ser | Gln |
|     | 675 |     |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| Ile | Asp | Asp | Leu | Tyr | Ser | Thr | Ile | Lys | Val |     |     |     |     |     |     |
|     | 690 |     |     |     |     | 695 |     |     |     |     |     |     |     |     |     |

&lt;210&gt; SEQ ID NO 81

&lt;211&gt; LENGTH: 737

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: human

&lt;220&gt; FEATURE:

&lt;221&gt; NAME/KEY: CDS

&lt;222&gt; LOCATION: (30) ... (662)

-continued

&lt;400&gt; SEQUENCE: 81

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ggagtttcgc cgccgcagtc ttcgccacc atg ccg ccc tac acc gtg gtc tat      53
                               Met Pro Pro Tyr Thr Val Val Tyr
                               1           5

ttc cca gtt cga ggc cgc tgc gcg gcc ctg cgc atg ctg ctg gca gat      101
Phe Pro Val Arg Gly Arg Cys Ala Ala Leu Arg Met Leu Leu Ala Asp
    10           15           20

cag ggc cag agc tgg aag gag gag gtg gtg acc gtg gag acg tgg cag      149
Gln Gly Gln Ser Trp Lys Glu Glu Val Val Thr Val Glu Thr Trp Gln
    25           30           35           40

gag ggc tca ctc aaa gcc tcc tgc cta tac ggg cag ctc ccc aag ttc      197
Glu Gly Ser Leu Lys Ala Ser Cys Leu Tyr Gly Gln Leu Pro Lys Phe
    45           50           55

cag gac gga gac ctc acc ctg tac cag tcc aat acc atc ctg cgt cac      245
Gln Asp Gly Asp Leu Thr Leu Tyr Gln Ser Asn Thr Ile Leu Arg His
    60           65           70

ctg ggc cgc acc ctt ggg ctc tat ggg aag gac cag cag gag gca gcc      293
Leu Gly Arg Thr Leu Gly Leu Tyr Gly Lys Asp Gln Gln Glu Ala Ala
    75           80           85

ctg gtg gac atg gtg aat gac ggc gtg gag gac ctc cgc tgc aaa tac      341
Leu Val Asp Met Val Asn Asp Gly Val Glu Asp Leu Arg Cys Lys Tyr
    90           95           100

atc tcc ctc atc tac acc aac tat gag gcg ggc aag gat gac tat gtg      389
Ile Ser Leu Ile Tyr Thr Asn Tyr Glu Ala Gly Lys Asp Asp Tyr Val
    105           110           115           120

aag gca ctg ccc ggg caa ctg aag cct ttt gag acc ctg ctg tcc cag      437
Lys Ala Leu Pro Gly Gln Leu Lys Pro Phe Glu Thr Leu Leu Ser Gln
    125           130           135

aac cag gga ggc aag acc ttc att gtg gga gac cag atc tcc ttc gct      485
Asn Gln Gly Gly Lys Thr Phe Ile Val Gly Asp Gln Ile Ser Phe Ala
    140           145           150

gac tac aac ctg ctg gac ttg ctg ctg atc cat gag gtc cta gcc cct      533
Asp Tyr Asn Leu Leu Asp Leu Leu Ile His Glu Val Leu Ala Pro
    155           160           165

ggc tgc ctg gat gcg ttc ccc ctg ctc tca gca tat gtg ggg cgc ctc      581
Gly Cys Leu Asp Ala Phe Pro Leu Leu Ser Ala Tyr Val Gly Arg Leu
    170           175           180

agc gcc cgg ccc aag ctc aag gcc ttc ctg gcc tcc cct gag tac gtg      629
Ser Ala Arg Pro Lys Leu Lys Ala Phe Leu Ala Ser Pro Glu Tyr Val
    185           190           195           200

aac ctc ccc atc aat ggc aac ggg aaa cag tga ggggtggggg gactctgagc      682
Asn Leu Pro Ile Asn Gly Asn Gly Lys Gln *
    205           210

gggaggcaga gtttcgcttc ctttctccag gaccaataaa atttctaaga gagct      737

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&lt;210&gt; SEQ ID NO 82

&lt;211&gt; LENGTH: 210

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 82

```

Met Pro Pro Tyr Thr Val Val Tyr Phe Pro Val Arg Gly Arg Cys Ala
1           5           10           15

Ala Leu Arg Met Leu Leu Ala Asp Gln Gly Gln Ser Trp Lys Glu Glu
20           25           30

Val Val Thr Val Glu Thr Trp Gln Glu Gly Ser Leu Lys Ala Ser Cys

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| 35                                                                |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |     |     |
|-------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu                                                               | Tyr | Gly | Gln | Leu | Pro | Lys | Phe | Gln | Asp | Gly | Asp | Leu | Thr | Leu | Tyr |
| 50                                                                |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |     |
| Gln                                                               | Ser | Asn | Thr | Ile | Leu | Arg | His | Leu | Gly | Arg | Thr | Leu | Gly | Leu | Tyr |
| 65                                                                |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Gly                                                               | Lys | Asp | Gln | Gln | Glu | Ala | Ala | Leu | Val | Asp | Met | Val | Asn | Asp | Gly |
|                                                                   |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Val                                                               | Glu | Asp | Leu | Arg | Cys | Lys | Tyr | Ile | Ser | Leu | Ile | Tyr | Thr | Asn | Tyr |
|                                                                   |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Glu                                                               | Ala | Gly | Lys | Asp | Asp | Tyr | Val | Lys | Ala | Leu | Pro | Gly | Gln | Leu | Lys |
|                                                                   |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Pro                                                               | Phe | Glu | Thr | Leu | Leu | Ser | Gln | Asn | Gln | Gly | Gly | Lys | Thr | Phe | Ile |
|                                                                   |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |
| Val                                                               | Gly | Asp | Gln | Ile | Ser | Phe | Ala | Asp | Tyr | Asn | Leu | Leu | Asp | Leu | Leu |
| 145                                                               |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Leu                                                               | Ile | His | Glu | Val | Leu | Ala | Pro | Gly | Cys | Leu | Asp | Ala | Phe | Pro | Leu |
|                                                                   |     |     | 165 |     |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Leu                                                               | Ser | Ala | Tyr | Val | Gly | Arg | Leu | Ser | Ala | Arg | Pro | Lys | Leu | Lys | Ala |
|                                                                   |     |     | 180 |     |     |     | 185 |     |     |     |     |     | 190 |     |     |
| Phe                                                               | Leu | Ala | Ser | Pro | Glu | Tyr | Val | Asn | Leu | Pro | Ile | Asn | Gly | Asn | Gly |
|                                                                   |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Lys                                                               | Gln |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 210                                                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <210> SEQ ID NO 83                                                |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <211> LENGTH: 704                                                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <212> TYPE: DNA                                                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <213> ORGANISM: human                                             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <220> FEATURE:                                                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <221> NAME/KEY: CDS                                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <222> LOCATION: (104) ... (568)                                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| <400> SEQUENCE: 83                                                |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| tgcagcgggtg gtcggctgtt ggggtgtggag tttcccagcg ccctcgggt cgcaccttt |     |     |     |     |     |     |     |     |     |     |     |     |     | 60  |     |
| gagcgttctg ctccggcgcc agcctacctc gctcctcggc gcc atg acc aca acc   |     |     |     |     |     |     |     |     |     |     |     |     |     | 115 |     |
| Met Thr Thr Thr                                                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 1                                                                 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| acc acc ttc aag gga gtc gac ccc aac agc agg aat agc tcc cga gtt   |     |     |     |     |     |     |     |     |     |     |     |     |     | 163 |     |
| Thr Thr Phe Lys Gly Val Asp Pro Asn Ser Arg Asn Ser Ser Arg Val   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 5 10 15 20                                                        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| ttg cgg cct cca ggt ggt gga tcc aat ttt tca tta ggt ttt gat gaa   |     |     |     |     |     |     |     |     |     |     |     |     |     | 211 |     |
| Leu Arg Pro Pro Gly Gly Gly Ser Asn Phe Ser Leu Gly Phe Asp Glu   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 25 30 35                                                          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| cca aca gaa caa cct gtg agg aag aac aaa atg gcc tct aat atc ttt   |     |     |     |     |     |     |     |     |     |     |     |     |     | 259 |     |
| Pro Thr Glu Gln Pro Val Arg Lys Asn Lys Met Ala Ser Asn Ile Phe   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 40 45 50                                                          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| ggg aca cct gaa gaa aat caa gct tct tgg gcc aag tca gca ggt gcc   |     |     |     |     |     |     |     |     |     |     |     |     |     | 307 |     |
| Gly Thr Pro Glu Glu Asn Gln Ala Ser Trp Ala Lys Ser Ala Gly Ala   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 55 60 65                                                          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| aag tct agt ggt ggc agg gaa gac ttg gag tca tct gga ctg cag aga   |     |     |     |     |     |     |     |     |     |     |     |     |     | 355 |     |
| Lys Ser Ser Gly Gly Arg Glu Asp Leu Glu Ser Ser Gly Leu Gln Arg   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 70 75 80                                                          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| agg aac tcc tct gaa gca agc tcc gga gac ttc tta gat ctg aag gga   |     |     |     |     |     |     |     |     |     |     |     |     |     | 403 |     |
| Arg Asn Ser Ser Glu Ala Ser Ser Gly Asp Phe Leu Asp Leu Lys Gly   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 85 90 95 100                                                      |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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gaa ggt gat att cat gaa aat gtg gac aca gac ttg cca ggc agc ctg      451
Glu Gly Asp Ile His Glu Asn Val Asp Thr Asp Leu Pro Gly Ser Leu
              105              110              115

ggg cag agt gaa gag aag ccc gtg cct gct gcg cct gtg ccc agc ccg      499
Gly Gln Ser Glu Glu Lys Pro Val Pro Ala Ala Pro Val Pro Ser Pro
              120              125              130

gtg gcc ccg gcc cca gtg cca tcc aga aga aat ccc cct ggc ggc aag      547
Val Ala Pro Ala Pro Val Pro Ser Arg Arg Asn Pro Pro Gly Gly Lys
              135              140              145

tcc agc ctc gtc ttg ggt tag ctctgactgt cctgaacgct gtcgttctgt      598
Ser Ser Leu Val Leu Gly *
              150

ctgtttcctc catgcttgag aactgcacaa cttgagcctg actgtacatc ttcttggatt      658

tgtttcatta aaaagaagca ctttatgtaa aaaaaaaaaa aaaaaa      704

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<210> SEQ ID NO 84
<211> LENGTH: 154
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 84

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Met Thr Thr Thr Thr Thr Phe Lys Gly Val Asp Pro Asn Ser Arg Asn
1      5      10      15

Ser Ser Arg Val Leu Arg Pro Pro Gly Gly Gly Ser Asn Phe Ser Leu
20     25     30

Gly Phe Asp Glu Pro Thr Glu Gln Pro Val Arg Lys Asn Lys Met Ala
35     40     45

Ser Asn Ile Phe Gly Thr Pro Glu Glu Asn Gln Ala Ser Trp Ala Lys
50     55     60

Ser Ala Gly Ala Lys Ser Ser Gly Gly Arg Glu Asp Leu Glu Ser Ser
65     70     75     80

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

Asp Leu Lys Gly Glu Gly Asp Ile His Glu Asn Val Asp Thr Asp Leu
100    105    110

Pro Gly Ser Leu Gly Gln Ser Glu Glu Lys Pro Val Pro Ala Ala Pro
115    120    125

Val Pro Ser Pro Val Ala Pro Ala Pro Val Pro Ser Arg Arg Asn Pro
130    135    140

Pro Gly Gly Lys Ser Ser Leu Val Leu Gly
145    150

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<210> SEQ ID NO 85
<211> LENGTH: 748
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (8)...(355)

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<400> SEQUENCE: 85

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ggccgcg atg agc ggg gag ccg ggg cag acg tcc gta gcg ccc cct ccc      49
Met Ser Gly Glu Pro Gly Gln Thr Ser Val Ala Pro Pro Pro
1      5      10

gag gag gtc gag ccg ggc agt ggg gtc cgc atc gtg gtg gag tac tgt      97
Glu Glu Val Glu Pro Gly Ser Gly Val Arg Ile Val Val Glu Tyr Cys
15     20     25     30

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gaa ccc tgc ggc ttc gag gcg acc tac ctg gag ctg gcc agt gct gtg      145
Glu Pro Cys Gly Phe Glu Ala Thr Tyr Leu Glu Leu Ala Ser Ala Val
                35                40                45

aag gag cag tat ccg ggc atc gag atc gag tcg cgc ctc ggg ggc aca      193
Lys Glu Gln Tyr Pro Gly Ile Glu Ile Glu Ser Arg Leu Gly Gly Thr
                50                55                60

ggg gcc ttt gag ata gag ata aat gga cag ctg gtg ttc tcc aag ctg      241
Gly Ala Phe Glu Ile Glu Ile Asn Gly Gln Leu Val Phe Ser Lys Leu
                65                70                75

gag aat ggg ggc ttt ccc tat gag aaa gat ctc att gag gcc atc cga      289
Glu Asn Gly Gly Phe Pro Tyr Glu Lys Asp Leu Ile Glu Ala Ile Arg
                80                85                90

aga gcc agt aat gga gaa acc cta gaa aag atc acc aac agc cgt cct      337
Arg Ala Ser Asn Gly Glu Thr Leu Glu Lys Ile Thr Asn Ser Arg Pro
                95                100                105                110

ccc tgc gtc atc ctg tga ctgcacagga ctctggggttc ctgctctgtt      385
Pro Cys Val Ile Leu *
                115

ctgggggtcca aaccttggtc tccctttggt cctgctggga gctccccctg cctctttccc      445

ctacttagct ccttagcaaa gagaccctgg cctccacttt gccctttggg taaaaagaag      505

gaatagaaga ttccgtggcc ttgggggag gagagagaca ctctccatga acatttctcc      565

agccacctca taccctcttc ccagggttaag tgcccacgaa agcccagtcc actcttcgcc      625

tcggtaatac ctgtctgatg ccacagattt tatttattct cccctaacc agggcaatgt      685

cagctattgg cagtaaaagt gcgctacaaa cactaaaaaa aaaaaaaaaa aaaaaaaaaa      745
aaa                                                                 748

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<210> SEQ ID NO 86
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 86

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Met Ser Gly Glu Pro Gly Gln Thr Ser Val Ala Pro Pro Pro Glu Glu
1          5          10          15

Val Glu Pro Gly Ser Gly Val Arg Ile Val Val Glu Tyr Cys Glu Pro
20         25         30

Cys Gly Phe Glu Ala Thr Tyr Leu Glu Leu Ala Ser Ala Val Lys Glu
35         40         45

Gln Tyr Pro Gly Ile Glu Ile Glu Ser Arg Leu Gly Gly Thr Gly Ala
50         55         60

Phe Glu Ile Glu Ile Asn Gly Gln Leu Val Phe Ser Lys Leu Glu Asn
65         70         75         80

Gly Gly Phe Pro Tyr Glu Lys Asp Leu Ile Glu Ala Ile Arg Arg Ala
85         90         95

Ser Asn Gly Glu Thr Leu Glu Lys Ile Thr Asn Ser Arg Pro Pro Cys
100        105        110

Val Ile Leu
115

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<210> SEQ ID NO 87
<211> LENGTH: 3020
<212> TYPE: DNA
<213> ORGANISM: human

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<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (111) ... (1295)

<400> SEQUENCE: 87

tgaagctcgt cagttcacca tccgcctcgt gcttcgcggg ggcgctgggc cgccagcctc   60
ggcaccgtcc tttcctttct ccctcgcgtt aggcaggtga cagcagggac atg tct   116
                               Met Ser
                               1

cgg gag atg cag gat gta gac ctc gct gag gtg aag cct ttg gtg gag   164
Arg Glu Met Gln Asp Val Asp Leu Ala Glu Val Lys Pro Leu Val Glu
      5              10              15

aaa ggg gag acc atc acc ggc ctc ctg caa gag ttt gat gtc cag gag   212
Lys Gly Glu Thr Ile Thr Gly Leu Leu Gln Glu Phe Asp Val Gln Glu
      20              25              30

cag gac atc gag act tta cat ggc tct gtt cac gtc acg ctg tgt ggg   260
Gln Asp Ile Glu Thr Leu His Gly Ser Val His Val Thr Leu Cys Gly
      35              40              45              50

act ccc aag gga aac cgg cct gtc atc ctc acc tac cat gac atc ggc   308
Thr Pro Lys Gly Asn Arg Pro Val Ile Leu Thr Tyr His Asp Ile Gly
      55              60              65

atg aac cac aaa acc tgc tac aac ccc ctc ttc aac tac gag gac atg   356
Met Asn His Lys Thr Cys Tyr Asn Pro Leu Phe Asn Tyr Glu Asp Met
      70              75              80

cag gag atc acc cag cac ttt gcc gtc tgc cac gtg gac gcc cct ggc   404
Gln Glu Ile Thr Gln His Phe Ala Val Cys His Val Asp Ala Pro Gly
      85              90              95

cag cag gac ggc gca gcc tcc ttc ccc gca ggg tac atg tac ccc tcc   452
Gln Gln Asp Gly Ala Ala Ser Phe Pro Ala Gly Tyr Met Tyr Pro Ser
      100             105             110

atg gat cag ctg gct gaa atg ctt cct gga gtc ctt caa cag ttt ggg   500
Met Asp Gln Leu Ala Glu Met Leu Pro Gly Val Leu Gln Gln Phe Gly
      115             120             125             130

ctg aaa agc att att ggc atg gga aca gga gca ggc gcc tac acc cta   548
Leu Lys Ser Ile Ile Gly Met Gly Thr Gly Ala Gly Ala Tyr Thr Leu
      135             140             145

act cga ttt gct cta aac aac cct gag atg gtg gag ggc ctt gtc ctt   596
Thr Arg Phe Ala Leu Asn Asn Pro Glu Met Val Glu Gly Leu Val Leu
      150             155             160

atc aac gtg aac cct tgt gcg gaa ggc tgg atg gac tgg gcc gcc tcc   644
Ile Asn Val Asn Pro Cys Ala Glu Gly Trp Met Asp Trp Ala Ala Ser
      165             170             175

aag atc tca gga tgg acc caa gct ctg ccg gac atg gtg gtg tcc cac   692
Lys Ile Ser Gly Trp Thr Gln Ala Leu Pro Asp Met Val Val Ser His
      180             185             190

ctt ttt ggg aag gaa gaa atg cag agt aac gtg gaa gtg gtc cac acc   740
Leu Phe Gly Lys Glu Glu Met Gln Ser Asn Val Glu Val Val His Thr
      195             200             205             210

tac cgc cag cac att gtg aat gac atg aac ccc ggc aac ctg cac ctg   788
Tyr Arg Gln His Ile Val Asn Asp Met Asn Pro Gly Asn Leu His Leu
      215             220             225

ttc atc aat gcc tac aac agc cgg cgc gac ctg gag att gag cga cca   836
Phe Ile Asn Ala Tyr Asn Ser Arg Arg Asp Leu Glu Ile Glu Arg Pro
      230             235             240

atg ccg gga acc cac aca gtc acc ctg cag tgc cct gct ctg ttg gtg   884
Met Pro Gly Thr His Thr Val Thr Leu Gln Cys Pro Ala Leu Leu Val
      245             250             255

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|                                                                     |      |
|---------------------------------------------------------------------|------|
| ggt ggg gac agc tgc cct gca gtg gat gcc gtg gtg gag tgc aac tca     | 932  |
| Val Gly Asp Ser Ser Pro Ala Val Asp Ala Val Val Glu Cys Asn Ser     |      |
| 260 265 270                                                         |      |
| aaa ttg gac cca aca aag acc act ctc ctc aag atg gcg gac tgt ggc     | 980  |
| Lys Leu Asp Pro Thr Lys Thr Thr Leu Leu Lys Met Ala Asp Cys Gly     |      |
| 275 280 285 290                                                     |      |
| ggc ctc ccg cag atc tcc cag ccg gcc aag ctc gct gag gcc ttc aag     | 1028 |
| Gly Leu Pro Gln Ile Ser Gln Pro Ala Lys Leu Ala Glu Ala Phe Lys     |      |
| 295 300 305                                                         |      |
| tac ttc gtg cag ggc atg gga tac atg ccc tgc gct agc atg acc cgc     | 1076 |
| Tyr Phe Val Gln Gly Met Gly Tyr Met Pro Ser Ala Ser Met Thr Arg     |      |
| 310 315 320                                                         |      |
| ctg atg cgg tcc cgc aca gcc tct ggt tcc agc gtc act tct ctg gat     | 1124 |
| Leu Met Arg Ser Arg Thr Ala Ser Gly Ser Ser Val Thr Ser Leu Asp     |      |
| 325 330 335                                                         |      |
| ggc acc cgc agc cgc tcc cac acc agc gag ggc acc cga agc cgc tcc     | 1172 |
| Gly Thr Arg Ser Arg Ser His Thr Ser Glu Gly Thr Arg Ser Arg Ser     |      |
| 340 345 350                                                         |      |
| cac acc agc gag ggc acc cgc agc cgc tgc cac acc agc gag ggg gcc     | 1220 |
| His Thr Ser Glu Gly Thr Arg Ser Arg Ser His Thr Ser Glu Gly Ala     |      |
| 355 360 365 370                                                     |      |
| cac ctg gac atc acc ccc aac tgc ggt gct gct ggg aac agc gcc ggg     | 1268 |
| His Leu Asp Ile Thr Pro Asn Ser Gly Ala Ala Gly Asn Ser Ala Gly     |      |
| 375 380 385                                                         |      |
| ccc aag tcc atg gag gtc tcc tgc tag gcggcctgcc cagctgccgc           | 1315 |
| Pro Lys Ser Met Glu Val Ser Cys *                                   |      |
| 390                                                                 |      |
| ccccggaactc tgatctctgt agtggccccc tctcccccg ccccttttcg cccctgect    | 1375 |
| gccatactgc gcctaactcg gtattaatcc aaagcttatt ttgtaagagt gagctctggt   | 1435 |
| ggagacaaat gaggtctatt acgtgggtgc cctctccaaa ggccgggttg cggtggacca   | 1495 |
| aaggaaggaa gcaagcatct ccgcatcgca tctctttcca ttaaccagtg gccggttgcc   | 1555 |
| actctcctcc cctccctcag agacacccaaa ctgccaaaaa caagacgcgt agcagcacac  | 1615 |
| acttcacaaa gccaagccta ggccgccctg agcatcctgg ttcaaacggg tgccctggtca  | 1675 |
| gaaggccagc cgcacacttc ccgtttcttc ttttaactgag gagaagctga tccagctttc  | 1735 |
| cggaacaaaa atcctttttc tcatttgggg aggggggtaa tagtgacatg caggcacctc   | 1795 |
| ttttaaacag gcaaaacagg aagggggaaa aggtgggatt catgtcgagg ctagaggcat   | 1855 |
| ttggaacaac aaatctacgt agttaacttg aagaaaccga tttttaaaagt tgggtgcatct | 1915 |
| agaaagcttt gaatgcagaa gcaaacaagc ttgatttttc tagcatcctc ttaatgtgca   | 1975 |
| gcaaaagcag gcaacaaaat ctccctggctt tacagacaaa aatatttcag caaacgttgg  | 2035 |
| gcatcatggt ttttgaaggc ttttagttctg ctttctgcct ctctccaca gcccacac     | 2095 |
| ccccccctg atacatgagc cagtgtattat tcttgttcag ggagaagatc atttagattt   | 2155 |
| gttttgcaat ccttagaatg gagggcaaca ttccacagct gccctggctg tgatgagtgt   | 2215 |
| ccttgacagg gccggagtag gagcaactgg gtgggggcgg aattgggggt actcgatgta   | 2275 |
| agggtatcct tgttgttgtg ttgagatcca gtgcagttgt gatttctgtg gatccagct    | 2335 |
| tgggtccagga attttgagag attggcttaa atccagtttt caatcttcga cagctgggct  | 2395 |
| ggaacgtgaa ctcatgagct gaacctgtct gaccgggtca cgttcttgga tctcagaac    | 2455 |
| tctttgctct tgtcgggggtg ggggtgggaa ctacgtggg gagcgggtggc tgagaaaatg  | 2515 |

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taaggattct ggaatacata ttccatggac tttccttccc tctcctgctt cctcttttcc 2575
tgctccctaa cctttcgccg aatggggcag acaaacactg acgtttcttg gtggccagtg 2635
cggtgccag gtctcgttac tactgccttg tacttttcat tttggctcac cgtggatttt 2695
ctcatagga gtttggctag agtgaattga atattgtaag tcagccactg ggacccgagg 2755
atctctggga ccccgagctt gggaggagga agtagtccag ccttcaggt gggcgtgaga 2815
ggcaatgact cgttacctgc cgcccatcac cttggaggcc ttccctggcc ttgagtagaa 2875
aagtcgggga tcggggcaag agaggctgag tacggatggg aaactattgt gcacaagtct 2935
ttccagagga gtttcttaat gagatatttg tatttatttc cagaccaata aatttgtaac 2995
ttgcaaaaa aaaaaaaaa aaaaa 3020

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&lt;210&gt; SEQ ID NO 88

&lt;211&gt; LENGTH: 394

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: human

&lt;400&gt; SEQUENCE: 88

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Met Ser Arg Glu Met Gln Asp Val Asp Leu Ala Glu Val Lys Pro Leu
1           5           10           15
Val Glu Lys Gly Glu Thr Ile Thr Gly Leu Leu Gln Glu Phe Asp Val
20          25          30
Gln Glu Gln Asp Ile Glu Thr Leu His Gly Ser Val His Val Thr Leu
35          40          45
Cys Gly Thr Pro Lys Gly Asn Arg Pro Val Ile Leu Thr Tyr His Asp
50          55          60
Ile Gly Met Asn His Lys Thr Cys Tyr Asn Pro Leu Phe Asn Tyr Glu
65          70          75          80
Asp Met Gln Glu Ile Thr Gln His Phe Ala Val Cys His Val Asp Ala
85          90          95
Pro Gly Gln Gln Asp Gly Ala Ala Ser Phe Pro Ala Gly Tyr Met Tyr
100         105         110
Pro Ser Met Asp Gln Leu Ala Glu Met Leu Pro Gly Val Leu Gln Gln
115         120         125
Phe Gly Leu Lys Ser Ile Ile Gly Met Gly Thr Gly Ala Gly Ala Tyr
130         135         140
Thr Leu Thr Arg Phe Ala Leu Asn Asn Pro Glu Met Val Glu Gly Leu
145         150         155         160
Val Leu Ile Asn Val Asn Pro Cys Ala Glu Gly Trp Met Asp Trp Ala
165         170         175
Ala Ser Lys Ile Ser Gly Trp Thr Gln Ala Leu Pro Asp Met Val Val
180         185         190
Ser His Leu Phe Gly Lys Glu Glu Met Gln Ser Asn Val Glu Val Val
195         200         205
His Thr Tyr Arg Gln His Ile Val Asn Asp Met Asn Pro Gly Asn Leu
210         215         220
His Leu Phe Ile Asn Ala Tyr Asn Ser Arg Arg Asp Leu Glu Ile Glu
225         230         235         240
Arg Pro Met Pro Gly Thr His Thr Val Thr Leu Gln Cys Pro Ala Leu
245         250         255
Leu Val Val Gly Asp Ser Ser Pro Ala Val Asp Ala Val Val Glu Cys
260         265         270

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Asn Ser Lys Leu Asp Pro Thr Lys Thr Thr Leu Leu Lys Met Ala Asp  
 275 280 285  
 Cys Gly Gly Leu Pro Gln Ile Ser Gln Pro Ala Lys Leu Ala Glu Ala  
 290 295 300  
 Phe Lys Tyr Phe Val Gln Gly Met Gly Tyr Met Pro Ser Ala Ser Met  
 305 310 315 320  
 Thr Arg Leu Met Arg Ser Arg Thr Ala Ser Gly Ser Ser Val Thr Ser  
 325 330 335  
 Leu Asp Gly Thr Arg Ser Arg Ser His Thr Ser Glu Gly Thr Arg Ser  
 340 345 350  
 Arg Ser His Thr Ser Glu Gly Thr Arg Ser Arg Ser His Thr Ser Glu  
 355 360 365  
 Gly Ala His Leu Asp Ile Thr Pro Asn Ser Gly Ala Ala Gly Asn Ser  
 370 375 380  
 Ala Gly Pro Lys Ser Met Glu Val Ser Cys  
 385 390

<210> SEQ ID NO 89  
 <211> LENGTH: 2401  
 <212> TYPE: DNA  
 <213> ORGANISM: human  
 <220> FEATURE:  
 <221> NAME/KEY: CDS  
 <222> LOCATION: (301) ... (762)

<400> SEQUENCE: 89

```

gcgtccccga agaggccggg aacggagccc aggaaaaact acaactccca ggaggcgctcg      60
ggagggcccg cccggagcca gcggaagaaa ctacaactcc cagaaggcgt cgggcgtgcc      120
ggcgcggggc ggtgacgtac ggggaccggc gcggagcgct gattcggccg gagctgccag      180
cggggaggct gcagcccgcg gttgttacag ctgctggagc agcagcgggc cccgctcccg      240
ggaaccgttc ccgggcccgt gatcttcggc cccacacgaa cagcagagag gggcagcagg      300
atg aat gtg ggc aca gcg cac agc gag gtg aac ccc aac acg cgg gtg      348
Met Asn Val Gly Thr Ala His Ser Glu Val Asn Pro Asn Thr Arg Val
1      5      10      15
atg aac agc cgt ggc atc tgg ctc tcc tac gtg ctg gcc atc ggt ctc      396
Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu
20      25      30
ctc cac atc gtg ctg ctg agc atc ccg ttt gtg agt gtc cct gtc gtc      444
Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val
35      40      45
tgg acc ctc acc aac ctc att cac aac atg ggc atg tat atc ttc ctg      492
Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu
50      55      60
cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag gcg      540
His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala
65      70      75      80
agg ctg cta acc cac tgg gag cag atg gat tat ggg gtc cag ttc acg      588
Arg Leu Leu Thr His Trp Glu Gln Met Asp Tyr Gly Val Gln Phe Thr
85      90      95
gcc tct cgg aag ttc ttg acc atc aca ccc atc gtg ctg tac ttc ctc      636
Ala Ser Arg Lys Phe Leu Thr Ile Thr Pro Ile Val Leu Tyr Phe Leu
100      105      110
acc agc ttc tac act aag tac gac cag atc cat ttt gtg ctc aac acc      684
Thr Ser Phe Tyr Thr Lys Tyr Asp Gln Ile His Phe Val Leu Asn Thr

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| 115                                                                 | 120 | 125 |      |
|---------------------------------------------------------------------|-----|-----|------|
| gtg tcc ctg atg agc gtg ctt atc ccc aag ctg ccc cag ctc cac gga     |     |     | 732  |
| Val Ser Leu Met Ser Val Leu Ile Pro Lys Leu Pro Gln Leu His Gly     |     |     |      |
| 130                                                                 | 135 | 140 |      |
| gtc cgg att ttt gga atc aat aag tac tga gagtgcagcc ccttccccctg      |     |     | 782  |
| Val Arg Ile Phe Gly Ile Asn Lys Tyr *                               |     |     |      |
| 145                                                                 | 150 |     |      |
| cccaggggtgg caggggaggg gtagggtaaa aggcattgtgc tgcaacactg aagacagaaa |     |     | 842  |
| gaagaagcct ctggacactg ccagagatgg gggttgagcc tctggcctaa tttccccct    |     |     | 902  |
| cgttcccccc agtagccaac ttggagtagc ttgtagtggg gttgggtag gccccctggg    |     |     | 962  |
| ctctgacctt ttctgaattt ttgtatcttt tccttttgct ttttgaatag agactccatg   |     |     | 1022 |
| gagttgggtca tggaatgggc tgggctcctg ggctgaacat ggaccacgca gttgacgacag |     |     | 1082 |
| gagggccaggg gaaaaacccc tgctcacttg tttgccctca ggcagccaaa gcactttaac  |     |     | 1142 |
| ccttgcatag ggagcagagg gcggtacggc ttctggattg tttcactgtg attcctaggt   |     |     | 1202 |
| tttttcgatg ccacgcagtg tgtgcttttg tgtatggaag caagtgtggg atgggtcttt   |     |     | 1262 |
| gcctttcttg gtagggagct gtctaatacca agtcccaggc ttttggcagc ttctctgcaa  |     |     | 1322 |
| cccaccgtgg gtccctggtg ggagtgggga gggtcagggt ggggaaagat ggggtagagt   |     |     | 1382 |
| gtagatggct tggttccaga ggtgaggggg ccagggtgc tgccatcctg gcctggtgga    |     |     | 1442 |
| ggttggggag ctgtaggaga gctagttagt cgagacttag aagaatgggg ccacatagca   |     |     | 1502 |
| gcagaggact ggtgtaaggg agggaggggt agggacagaa gctagaccca atctcctttg   |     |     | 1562 |
| ggatgtgggc agggagggaa gcaggcttg agggttaatt taccacaga atgtgatagt     |     |     | 1622 |
| aataggggag ggaggtgct gtgggtttaa ctccctgggt ggctgttggg tagacagggtg   |     |     | 1682 |
| gggaaaaggc ccgtgagtca ttgtaagcac aggtccaact tggccctgac tctgcgggg    |     |     | 1742 |
| gtatggggaa gctgtgacag aaacgatggg tgctgtggtc ctctgcaggc cctcaccct    |     |     | 1802 |
| taacttcctc atacagactg gcaactgggca gggcctctca tgtggcagcc acatgtggcg  |     |     | 1862 |
| ttgtgaggcc accccatgtg gggctctgtg tgagagtct gtaggatccc tgcctaagca    |     |     | 1922 |
| gcacagagga aggggaaga cgtggcctgt aggcactgtc tcagcctgca gagaagaaag    |     |     | 1982 |
| tgaggccggg agcctgagcc tgggctggag ccttctcccc tccccagttg gactaggggc   |     |     | 2042 |
| agtgttaatt ttgaaaagg gtgggtccct gtgtcctct ccaggggtcc aagggaacag     |     |     | 2102 |
| gagaggtcac tgggcctggt ttctccctcc tgaccctgca tctccacccc cgtgtatcat   |     |     | 2162 |
| agggaaacttt caccttaaaa tctttctaag caaagtgtga ataggathtt tactcccttt  |     |     | 2222 |
| gtacagtatt ctgagaaacg caaataaaag ggcaacatgt ttctgtttcc ctgtgtctgg   |     |     | 2282 |
| ccttcgcttc ctggaaggct gaggggaggg ggcaggggtg tgggcagcgg ctcccgtga    |     |     | 2342 |
| ggtgctgggt gggcatcagt gcagctctga cgggtggcagg aggggcgctg ggactgctg   |     |     | 2401 |

<210> SEQ ID NO 90  
 <211> LENGTH: 153  
 <212> TYPE: PRN  
 <213> ORGANISM: human

<400> SEQUENCE: 90

Met Asn Val Gly Thr Ala His Ser Glu Val Asn Pro Asn Thr Arg Val  
 1 5 10 15

Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu

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| 20                             |     |     |     |     | 25   |      |     |     |     | 30   |     |     |     |     |       |   |     |     |     |
|--------------------------------|-----|-----|-----|-----|------|------|-----|-----|-----|------|-----|-----|-----|-----|-------|---|-----|-----|-----|
| Leu                            | His | Ile | Val | Leu | Leu  | Ser  | Ile | Pro | Phe | Val  | Ser | Val | Pro | Val | Val   |   |     |     |     |
|                                | 35  |     |     |     |      |      | 40  |     |     |      |     | 45  |     |     |       |   |     |     |     |
| Trp                            | Thr | Leu | Thr | Asn | Leu  | Ile  | His | Asn | Met | Gly  | Met | Tyr | Ile | Phe | Leu   |   |     |     |     |
|                                | 50  |     |     |     |      | 55   |     |     |     |      | 60  |     |     |     |       |   |     |     |     |
| His                            | Thr | Val | Lys | Gly | Thr  | Pro  | Phe | Glu | Thr | Pro  | Asp | Gln | Gly | Lys | Ala   |   |     |     |     |
| 65                             |     |     |     |     | 70   |      |     |     |     | 75   |     |     |     |     | 80    |   |     |     |     |
| Arg                            | Leu | Leu | Thr | His | Trp  | Glu  | Gln | Met | Asp | Tyr  | Gly | Val | Gln | Phe | Thr   |   |     |     |     |
|                                |     |     |     | 85  |      |      |     |     | 90  |      |     |     |     | 95  |       |   |     |     |     |
| Ala                            | Ser | Arg | Lys | Phe | Leu  | Thr  | Ile | Thr | Pro | Ile  | Val | Leu | Tyr | Phe | Leu   |   |     |     |     |
|                                |     |     | 100 |     |      |      |     | 105 |     |      |     |     | 110 |     |       |   |     |     |     |
| Thr                            | Ser | Phe | Tyr | Thr | Lys  | Tyr  | Asp | Gln | Ile | His  | Phe | Val | Leu | Asn | Thr   |   |     |     |     |
|                                |     | 115 |     |     |      |      | 120 |     |     |      |     | 125 |     |     |       |   |     |     |     |
| Val                            | Ser | Leu | Met | Ser | Val  | Leu  | Ile | Pro | Lys | Leu  | Pro | Gln | Leu | His | Gly   |   |     |     |     |
|                                | 130 |     |     |     |      | 135  |     |     |     |      | 140 |     |     |     |       |   |     |     |     |
| Val                            | Arg | Ile | Phe | Gly | Ile  | Asn  | Lys | Tyr |     |      |     |     |     |     |       |   |     |     |     |
| 145                            |     |     |     |     | 150  |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <210> SEQ ID NO 91             |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <211> LENGTH: 778              |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <212> TYPE: DNA                |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <213> ORGANISM: human          |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <220> FEATURE:                 |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <221> NAME/KEY: CDS            |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <222> LOCATION: (52) ... (711) |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| <400> SEQUENCE: 91             |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   |     |     |     |
| cagg                           | ttg | gaa | acc | agt | cccc | cagg | cg  | gc  | ga  | ggag | agc | ggt | gc  | ctt | gcagg | g | atg | ctg | 57  |
|                                |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   | Met | Leu |     |
|                                |     |     |     |     |      |      |     |     |     |      |     |     |     |     |       |   | 1   |     |     |
| cg                             | g   | g   | g   | g   | g    | a    | c   | c   | a   | acc  | ggg | gac | tta | ccc | cg    | g | g   | g   | 105 |
| Arg                            | Ala | Gly | Ala | Pro | Thr  | Gly  | Asp | Leu | Pro | Arg  | Ala | Gly | Glu | Val | His   |   |     |     |     |
|                                | 5   |     |     |     |      | 10   |     |     |     |      |     | 15  |     |     |       |   |     |     |     |
| acc                            | ggg | acc | acc | atc | atg  | gca  | gtg | gag | ttt | gac  | ggg | ggc | gtt | gtg | atg   |   |     |     | 153 |
| Thr                            | Gly | Thr | Thr | Ile | Met  | Ala  | Val | Glu | Phe | Asp  | Gly | Gly | Val | Val | Met   |   |     |     |     |
|                                | 20  |     |     |     |      | 25   |     |     |     |      | 30  |     |     |     |       |   |     |     |     |
| ggt                            | tct | gat | tcc | cga | gtg  | tct  | gca | ggc | gag | gcg  | gtg | gtg | aac | cga | gtg   |   |     |     | 201 |
| Gly                            | Ser | Asp | Ser | Arg | Val  | Ser  | Ala | Gly | Glu | Ala  | Val | Val | Asn | Arg | Val   |   |     |     |     |
|                                | 35  |     |     |     |      | 40   |     |     |     |      | 45  |     |     |     | 50    |   |     |     |     |
| ttt                            | gac | aag | ctg | tcc | ccg  | ctg  | cac | gag | cgc | atc  | tac | tgt | gca | ctc | tct   |   |     |     | 249 |
| Phe                            | Asp | Lys | Leu | Ser | Pro  | Leu  | His | Glu | Arg | Ile  | Tyr | Cys | Ala | Leu | Ser   |   |     |     |     |
|                                |     |     | 55  |     |      |      |     | 60  |     |      |     |     | 65  |     |       |   |     |     |     |
| ggt                            | tca | gct | gct | gat | gcc  | caa  | gcc | gtg | gcc | gac  | atg | gcc | gcc | tac | cag   |   |     |     | 297 |
| Gly                            | Ser | Ala | Ala | Asp | Ala  | Gln  | Ala | Val | Ala | Asp  | Met | Ala | Ala | Tyr | Gln   |   |     |     |     |
|                                |     | 70  |     |     |      |      | 75  |     |     |      |     | 80  |     |     |       |   |     |     |     |
| ctg                            | gag | ctc | cat | ggg | ata  | gaa  | ctg | gag | gaa | cct  | cca | ctt | gtt | ttg | gct   |   |     |     | 345 |
| Leu                            | Glu | Leu | His | Gly | Ile  | Glu  | Glu | Glu | Pro | Pro  | Leu | Val | Leu | Ala |       |   |     |     |     |
|                                |     | 85  |     |     |      | 90   |     |     |     |      | 95  |     |     |     |       |   |     |     |     |
| gct                            | gca | aat | gtg | gtg | aga  | aat  | atc | agc | tat | aaa  | tat | cga | gag | gac | ttg   |   |     |     | 393 |
| Ala                            | Ala | Asn | Val | Val | Arg  | Asn  | Ile | Ser | Tyr | Lys  | Tyr | Arg | Glu | Asp | Leu   |   |     |     |     |
|                                | 100 |     |     |     |      | 105  |     |     |     |      | 110 |     |     |     |       |   |     |     |     |
| tct                            | gca | cat | ctc | atg | gta  | gct  | ggc | tgg | gac | caa  | cgt | gaa | gga | ggc | cag   |   |     |     | 441 |
| Ser                            | Ala | His | Leu | Met | Val  | Ala  | Gly | Trp | Asp | Gln  | Arg | Glu | Gly | Gly | Gln   |   |     |     |     |
|                                | 115 |     |     |     |      | 120  |     |     |     |      | 125 |     |     |     | 130   |   |     |     |     |
| gta                            | tat | gga | acc | ctg | gga  | gga  | atg | ctg | act | cga  | cag | cct | ttt | gcc | att   |   |     |     | 489 |
| Val                            | Tyr | Gly | Thr | Thr | Gly  | Gly  | Met | Leu | Thr | Arg  | Gln | Pro | Phe | Ala | Ile   |   |     |     |     |
|                                |     |     |     | 135 |      |      |     |     | 140 |      |     |     |     | 145 |       |   |     |     |     |

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ggt ggc tcc ggc agc acc ttt atc tat ggt tat gtg gat gca gca tat      537
Gly Gly Ser Gly Ser Thr Phe Ile Tyr Gly Tyr Val Asp Ala Ala Tyr
      150                      155                      160

aag cca ggc atg tct ccc gag gag tgc agg cgc ttc acc aca gac gct      585
Lys Pro Gly Met Ser Pro Glu Glu Cys Arg Arg Phe Thr Thr Asp Ala
      165                      170                      175

att gct ctg gcc atg agc cgg gat ggc tca agc ggg ggt gtc atc tac      633
Ile Ala Leu Ala Met Ser Arg Asp Gly Ser Ser Gly Gly Val Ile Tyr
      180                      185                      190

ctg gtc act att aca gct gcc ggt gtg gac cat cga gtc atc ttg ggc      681
Leu Val Thr Ile Thr Ala Ala Gly Val Asp His Arg Val Ile Leu Gly
      195                      200                      205                      210

aat gaa ctg cca aaa ttc tat gat gag tga accttcccca gaattctctt      731
Asn Glu Leu Pro Lys Phe Tyr Asp Glu *
      215

tcttattttg taataaaactc tctagggcca aaaaaaaaaa aaaaaaa      778

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<210> SEQ ID NO 92
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: human

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<400> SEQUENCE: 92

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Met Leu Arg Ala Gly Ala Pro Thr Gly Asp Leu Pro Arg Ala Gly Glu
1      5      10      15

Val His Thr Gly Thr Thr Ile Met Ala Val Glu Phe Asp Gly Gly Val
20     25     30

Val Met Gly Ser Asp Ser Arg Val Ser Ala Gly Glu Ala Val Val Asn
35     40     45

Arg Val Phe Asp Lys Leu Ser Pro Leu His Glu Arg Ile Tyr Cys Ala
50     55     60

Leu Ser Gly Ser Ala Ala Asp Ala Gln Ala Val Ala Asp Met Ala Ala
65     70     75     80

Tyr Gln Leu Glu Leu His Gly Ile Glu Leu Glu Glu Pro Pro Leu Val
85     90     95

Leu Ala Ala Ala Asn Val Val Arg Asn Ile Ser Tyr Lys Tyr Arg Glu
100    105    110

Asp Leu Ser Ala His Leu Met Val Ala Gly Trp Asp Gln Arg Glu Gly
115    120    125

Gly Gln Val Tyr Gly Thr Leu Gly Gly Met Leu Thr Arg Gln Pro Phe
130    135    140

Ala Ile Gly Gly Ser Gly Ser Thr Phe Ile Tyr Gly Tyr Val Asp Ala
145    150    155    160

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

Asp Ala Ile Ala Leu Ala Met Ser Arg Asp Gly Ser Ser Gly Gly Val
180    185    190

Ile Tyr Leu Val Thr Ile Thr Ala Ala Gly Val Asp His Arg Val Ile
195    200    205

Leu Gly Asn Glu Leu Pro Lys Phe Tyr Asp Glu
210    215

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<210> SEQ ID NO 93
<211> LENGTH: 1374

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<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (103)...(1047)

<400> SEQUENCE: 93

ggacagcttg gagatagggc ccggaattgc gggcgctcact ctgctcctgc gacctagcca      60

ggcgtgaggg agtgacagca gcgcattcgc gggacgagag cg atg agt gag aac      114
                               Met Ser Glu Asn
                               1

gcc gca cca ggt ctg atc tca gag ctg aag ctg gct gtg ccc tgg ggc      162
Ala Ala Pro Gly Leu Ile Ser Glu Leu Lys Leu Ala Val Pro Trp Gly
5                               10                               15                               20

cac atc gca gcc aaa gcc tgg ggc tcc ctg cag ggc cct cca gtt ctc      210
His Ile Ala Ala Lys Ala Trp Gly Ser Leu Gln Gly Pro Pro Val Leu
                               25                               30                               35

tgc ctg cac ggc tgg ctg gac aat gcc agc tcc ttc gac aga ctc atc      258
Cys Leu His Gly Trp Leu Asp Asn Ala Ser Ser Phe Asp Arg Leu Ile
                               40                               45                               50

cct ctt ctc ccg caa gac ttt tat tac gtt gcc atg gat ttc gga ggt      306
Pro Leu Leu Pro Gln Asp Phe Tyr Tyr Val Ala Met Asp Phe Gly Gly
                               55                               60                               65

cat ggg ctc tcg tcc cat tac agc cca ggt gtc cca tat tac ctc cag      354
His Gly Leu Ser Ser His Tyr Ser Pro Gly Val Pro Tyr Tyr Leu Gln
70                               75                               80

act ttt gtg agt gag atc cga aga gtt gtg gca gcc ttg aaa tgg aat      402
Thr Phe Val Ser Glu Ile Arg Arg Val Val Ala Ala Leu Lys Trp Asn
85                               90                               95                               100

cga ttc tcc att ctg ggc cac agc ttc ggt ggc gtc gtg ggc gga atg      450
Arg Phe Ser Ile Leu Gly His Ser Phe Gly Gly Val Val Gly Gly Met
                               105                               110                               115

ttt ttc tgt acc ttc ccc gag atg gtg gat aaa ctt atc ttg ctg gac      498
Phe Phe Cys Thr Phe Pro Glu Met Val Asp Lys Leu Ile Leu Leu Asp
                               120                               125                               130

acg ccg ctc ttt ctc ctg gaa tca gat gaa atg gag aac ttg ctg acc      546
Thr Pro Leu Phe Leu Leu Glu Ser Asp Glu Met Glu Asn Leu Leu Thr
                               135                               140                               145

tac aag cgg aga gcc ata gag cac gtg ctg cag gta gag gcc tcc cag      594
Tyr Lys Arg Arg Ala Ile Glu His Val Leu Gln Val Glu Ala Ser Gln
150                               155                               160

gag ccc tcg cac gtg ttc agc ctg aag cag ctg ctg cag agg tta ctg      642
Glu Pro Ser His Val Phe Ser Leu Lys Gln Leu Leu Gln Arg Leu Leu
165                               170                               175                               180

aag agc aat agc cac ttg agt gag gag tgc ggg gag ctt ctc ctg caa      690
Lys Ser Asn Ser His Leu Ser Glu Cys Gly Glu Leu Leu Leu Gln
185                               190                               195

aga gga acc acg aag gtg gcc aca ggt ctg gtt ctg aac aga gac cag      738
Arg Gly Thr Thr Lys Val Ala Thr Gly Leu Val Leu Asn Arg Asp Gln
200                               205                               210

agg ctc gcc tgg gca gag aac agc att gac ttc atc agc agg gag ctg      786
Arg Leu Ala Trp Ala Glu Asn Ser Ile Asp Phe Ile Ser Arg Glu Leu
215                               220                               225

tgt gcg cat tcc atc agg aag ctg cag gcc cat gtc ctg ttg atc aaa      834
Cys Ala His Ser Ile Arg Lys Leu Gln Ala His Val Leu Leu Ile Lys
230                               235                               240

gca gtc cac gga tat ttt gat tca aga cag aat tac tct gag aag gag      882
Ala Val His Gly Tyr Phe Asp Ser Arg Gln Asn Tyr Ser Glu Lys Glu

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| 245                                                               | 250 | 255 | 260 |      |
|-------------------------------------------------------------------|-----|-----|-----|------|
| tcc ctg tcg ttc atg ata gac acg atg aaa tcc acc ctc aaa gag cag   |     |     |     | 930  |
| Ser Leu Ser Phe Met Ile Asp Thr Met Lys Ser Thr Leu Lys Glu Gln   |     |     |     |      |
|                                                                   | 265 | 270 | 275 |      |
| ttc cag ttt gtg gaa gtc cca ggc aat cac tgt gtc cac atg agc gaa   |     |     |     | 978  |
| Phe Gln Phe Val Glu Val Pro Gly Asn His Cys Val His Met Ser Glu   |     |     |     |      |
|                                                                   | 280 | 285 | 290 |      |
| ccc cag cac gtg gcc agt atc atc agc tcc ttc tta cag tgc aca cac   |     |     |     | 1026 |
| Pro Gln His Val Ala Ser Ile Ile Ser Ser Phe Leu Gln Cys Thr His   |     |     |     |      |
|                                                                   | 295 | 300 | 305 |      |
| atg ctc cca gcc cag ctg tag ctctgggcct ggaactatga agacctagt       |     |     |     | 1077 |
| Met Leu Pro Ala Gln Leu *                                         |     |     |     |      |
|                                                                   | 310 |     |     |      |
| ctccagact caacactggg actctgagtt cctgagcccc acaacaaggc cagggatggt  |     |     |     | 1137 |
| ggggacaggc ctactagtc ttgagggcca gcctaggatg gtagtcaggg gaaggagcga  |     |     |     | 1197 |
| gattccaact tcaacatctg tgacctcaag ggggagacag agtctgggtt ccagggctgc |     |     |     | 1257 |
| tttctctcgg ctaataataa atatccagcc agctggagga aggaagggca ggctgggccc |     |     |     | 1317 |
| acctagcctt tccctgctgc ccaactggat ggaaaataaa aggttcttgt attctca    |     |     |     | 1374 |
| <br><210> SEQ ID NO 94                                            |     |     |     |      |
| <211> LENGTH: 314                                                 |     |     |     |      |
| <212> TYPE: PRT                                                   |     |     |     |      |
| <213> ORGANISM: human                                             |     |     |     |      |
| <br><400> SEQUENCE: 94                                            |     |     |     |      |
| Met Ser Glu Asn Ala Ala Pro Gly Leu Ile Ser Glu Leu Lys Leu Ala   |     |     |     |      |
| 1 5 10 15                                                         |     |     |     |      |
| Val Pro Trp Gly His Ile Ala Ala Lys Ala Trp Gly Ser Leu Gln Gly   |     |     |     |      |
| 20 25 30                                                          |     |     |     |      |
| Pro Pro Val Leu Cys Leu His Gly Trp Leu Asp Asn Ala Ser Ser Phe   |     |     |     |      |
| 35 40 45                                                          |     |     |     |      |
| Asp Arg Leu Ile Pro Leu Leu Pro Gln Asp Phe Tyr Tyr Val Ala Met   |     |     |     |      |
| 50 55 60                                                          |     |     |     |      |
| Asp Phe Gly Gly His Gly Leu Ser Ser His Tyr Ser Pro Gly Val Pro   |     |     |     |      |
| 65 70 75 80                                                       |     |     |     |      |
| Tyr Tyr Leu Gln Thr Phe Val Ser Glu Ile Arg Arg Val Val Ala Ala   |     |     |     |      |
| 85 90 95                                                          |     |     |     |      |
| Leu Lys Trp Asn Arg Phe Ser Ile Leu Gly His Ser Phe Gly Gly Val   |     |     |     |      |
| 100 105 110                                                       |     |     |     |      |
| Val Gly Gly Met Phe Phe Cys Thr Phe Pro Glu Met Val Asp Lys Leu   |     |     |     |      |
| 115 120 125                                                       |     |     |     |      |
| Ile Leu Leu Asp Thr Pro Leu Phe Leu Leu Glu Ser Asp Glu Met Glu   |     |     |     |      |
| 130 135 140                                                       |     |     |     |      |
| Asn Leu Leu Thr Tyr Lys Arg Arg Ala Ile Glu His Val Leu Gln Val   |     |     |     |      |
| 145 150 155 160                                                   |     |     |     |      |
| Glu Ala Ser Gln Glu Pro Ser His Val Phe Ser Leu Lys Gln Leu Leu   |     |     |     |      |
| 165 170 175                                                       |     |     |     |      |
| Gln Arg Leu Leu Lys Ser Asn Ser His Leu Ser Glu Glu Cys Gly Glu   |     |     |     |      |
| 180 185 190                                                       |     |     |     |      |
| Leu Leu Leu Gln Arg Gly Thr Thr Lys Val Ala Thr Gly Leu Val Leu   |     |     |     |      |
| 195 200 205                                                       |     |     |     |      |
| Asn Arg Asp Gln Arg Leu Ala Trp Ala Glu Asn Ser Ile Asp Phe Ile   |     |     |     |      |

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| 210                                                                | 215                                     | 220                 |     |
|--------------------------------------------------------------------|-----------------------------------------|---------------------|-----|
| Ser Arg Glu Leu Cys                                                | Ala His Ser Ile Arg Lys                 | Leu Gln Ala His Val |     |
| 225                                                                | 230                                     | 235                 | 240 |
| Leu Leu Ile Lys Ala Val                                            | His Gly Tyr Phe Asp Ser Arg Gln Asn Tyr |                     |     |
|                                                                    | 245                                     | 250                 | 255 |
| Ser Glu Lys Glu Ser Leu Ser Phe Met Ile Asp Thr Met Lys Ser Thr    |                                         |                     |     |
|                                                                    | 260                                     | 265                 | 270 |
| Leu Lys Glu Gln Phe Gln Phe Val Glu Val Pro Gly Asn His Cys Val    |                                         |                     |     |
|                                                                    | 275                                     | 280                 | 285 |
| His Met Ser Glu Pro Gln His Val Ala Ser Ile Ile Ser Ser Phe Leu    |                                         |                     |     |
|                                                                    | 290                                     | 295                 | 300 |
| Gln Cys Thr His Met Leu Pro Ala Gln Leu                            |                                         |                     |     |
| 305                                                                | 310                                     |                     |     |
| <210> SEQ ID NO 95                                                 |                                         |                     |     |
| <211> LENGTH: 598                                                  |                                         |                     |     |
| <212> TYPE: DNA                                                    |                                         |                     |     |
| <213> ORGANISM: human                                              |                                         |                     |     |
| <220> FEATURE:                                                     |                                         |                     |     |
| <221> NAME/KEY: CDS                                                |                                         |                     |     |
| <222> LOCATION: (23)...(421)                                       |                                         |                     |     |
| <400> SEQUENCE: 95                                                 |                                         |                     |     |
| cagagtcact cctgccttca cc atg aag tcc agc ggc ctc ttc ccc ttc ctg   |                                         |                     | 52  |
|                                                                    | Met Lys Ser Ser Gly Leu Phe Pro Phe Leu |                     |     |
|                                                                    | 1 5 10                                  |                     |     |
| gtg ctg ctt gcc ctg gga act ctg gca cct tgg gct gtg gaa ggc tct    |                                         |                     | 100 |
| Val Leu Leu Ala Leu Gly Thr Leu Ala Pro Trp Ala Val Glu Gly Ser    |                                         |                     |     |
|                                                                    | 15 20 25                                |                     |     |
| gga aag tcc ttc aaa gct gga gtc tgt cct cct aag aaa tct gcc cag    |                                         |                     | 148 |
| Gly Lys Ser Phe Lys Ala Gly Val Cys Pro Pro Lys Lys Ser Ala Gln    |                                         |                     |     |
|                                                                    | 30 35 40                                |                     |     |
| tgc ctt aga tac aag aaa cct gag tgc cag agt gac tgg cag tgt cca    |                                         |                     | 196 |
| Cys Leu Arg Tyr Lys Lys Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro    |                                         |                     |     |
|                                                                    | 45 50 55                                |                     |     |
| ggg aag aag aga tgt tgt cct gac act tgt ggc atc aaa tgc ctg gat    |                                         |                     | 244 |
| Gly Lys Lys Arg Cys Cys Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp    |                                         |                     |     |
|                                                                    | 60 65 70                                |                     |     |
| cct gtt gac acc cca aac cca aca agg agg aag cct ggg aag tgc cca    |                                         |                     | 292 |
| Pro Val Asp Thr Pro Asn Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro    |                                         |                     |     |
|                                                                    | 75 80 85 90                             |                     |     |
| gtg act tat ggc caa tgt ttg atg ctt aac ccc ccc aat ttc tgt gag    |                                         |                     | 340 |
| Val Thr Tyr Gly Gln Cys Leu Met Leu Asn Pro Pro Asn Phe Cys Glu    |                                         |                     |     |
|                                                                    | 95 100 105                              |                     |     |
| atg gat ggc cag tgc aag cgt gac ttg aag tgt tgc atg ggc atg tgt    |                                         |                     | 388 |
| Met Asp Gly Gln Cys Lys Arg Asp Leu Lys Cys Cys Met Gly Met Cys    |                                         |                     |     |
|                                                                    | 110 115 120                             |                     |     |
| ggg aaa tcc tgc gtt tcc cct gtg aaa gct tga ttctgccaat atggaggagg  |                                         |                     | 441 |
| Gly Lys Ser Cys Val Ser Pro Val Lys Ala *                          |                                         |                     |     |
|                                                                    | 125 130                                 |                     |     |
| ctctggagtc ctgctctgtg tgggtccaggt cctttccacc ctgagacttg gctccaccac |                                         |                     | 501 |
| tgatatacctc ctttggggaa aggccttgga cacagcaggc tttcaagaag tgccagttga |                                         |                     | 561 |
| tcaatgaata aataaacgag cctattttctc tttgcac                          |                                         |                     | 598 |

&lt;210&gt; SEQ ID NO 96

&lt;211&gt; LENGTH: 132

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<212> TYPE: PRT
<213> ORGANISM: human

<400> SEQUENCE: 96
Met Lys Ser Ser Gly Leu Phe Pro Phe Leu Val Leu Leu Ala Leu Gly
1           5           10           15
Thr Leu Ala Pro Trp Ala Val Glu Gly Ser Gly Lys Ser Phe Lys Ala
20          25          30
Gly Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys
35          40          45
Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
50          55          60
Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn
65          70          75          80
Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys
85          90          95
Leu Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys
100         105         110
Arg Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser
115         120         125
Pro Val Lys Ala
130

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What is claimed:

1. A method of assessing whether a patient is afflicted with breast cancer, the method comprising:

- a) determining the level of expression of a marker in a patient sample, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2;
- b) determining the level of expression of the marker in a control sample; and
- c) comparing the level of expression of the marker in the patient sample and the level of expression of the marker in the control sample,

wherein a difference between the level of expression of the marker in the patient sample as compared to the level of expression of the marker in the control sample is an indication that the patient is afflicted with breast cancer.

2. The method of claim 1, wherein the control sample comprises breast cells from the patient which are non-cancerous.

3. The method of claim 1, wherein the level of expression of the marker in the control sample is predetermined using an average of the levels of expression of the marker in samples from a population of subjects having indolent breast tumors or no breast tumors.

4. The method of claim 1, wherein the marker comprises a transcribed polynucleotide or portion thereof.

5. The method of claim 1, wherein the patient sample comprises cells obtained from the patient.

6. The method of claim 1, wherein the patient sample comprises a fluid selected from the group consisting of blood fluid, lymph, cystic fluid, nipple aspirates, and fluid collected from a lump biopsy.

7. The method of claim 1, wherein the level of expression of the marker in the patient sample is assessed by detecting the presence of a marker protein in the sample.

8. The method of claim 7, wherein the presence of the marker protein is detected using a reagent which specifically binds with the protein.

9. The method of claim 8, wherein the reagent is selected from the group consisting of an antibody, an antibody derivative, an antigen-binding antibody fragment, and a non-antibody peptide which specifically binds the protein.

10. The method of claim 9, wherein the antibody or antigen-binding antibody fragment is a monoclonal antibody or antigen-binding fragment thereof, or a polyclonal antibody or antigen-binding fragment thereof.

11. The method of claim 9, wherein the antibody or antigen-binding antibody fragment is labelled.

12. The method of claim 11, wherein the antibody or antigen-binding antibody fragment is radio-labelled, biotin-labelled, chromophore labelled, fluorophore labelled, or enzyme labelled.

13. The method of claim 1, wherein the level of expression of the marker in the patient sample is assessed by detecting the presence in the patient sample of a transcribed polynucleotide or portion thereof, corresponding to a nucleic acid marker.

14. The method of claim 13, wherein the transcribed polynucleotide is a mRNA or a cDNA.

15. The method of claim 13, wherein the step of detecting a transcribed polynucleotide further comprises amplifying the transcribed polynucleotide.

16. The method of claim 1, wherein the level of expression of the marker in the patient sample is assessed by detecting the presence in the patient sample of a transcribed polynucleotide.

otide which anneals with a nucleic acid marker or a portion thereof under stringent hybridization conditions.

**17.** The method of claim **1**, wherein the level of expression of the marker in the patient sample differs from the level of expression of the marker in the control sample by a factor selected from the group consisting of: a factor of at least about 2, a factor of at least about 3, a factor of at least about 4, and a factor of at least about 5.

**18.** The method of claim **1**, wherein the level of expression of the marker in the patient sample is assessed using a technique selected from the group consisting of: Northern hybridization, polymerase chain reaction analysis, RT-PCR, probe array and in situ hybridization.

**19.** A method of assessing whether a patient is afflicted with breast cancer, the method comprising:

- a) determining the level of expression in a patient sample of at least two markers independently selected from the markers listed in Table 1 and Table 2;
- b) determining the level of expression of each of the markers in a control sample; and
- c) comparing the level of expression of the marker in the patient sample and the level of expression of the marker in the control sample;

wherein a difference in the level of expression of more than one of the markers in the patient sample as compared to the corresponding level of expression of the markers in the control sample, is an indication that the patient is afflicted with breast cancer.

**20.** The method of claim **19**, wherein the level of expression of at least three markers or at least five markers is determined.

**21.** A method for assessing whether a patient has breast cancer that has metastasized or is likely to metastasize, comprising:

- a) determining the level of expression of a marker in a patient sample, wherein the marker is selected from the markers listed in Table 2,
- b) determining the level of expression of the marker in a control sample, and
- c) comparing the level of expression of the marker in the patient sample and the level of expression of the marker in the control sample;

wherein a higher level of expression in the patient sample as compared to the level of expression of the marker in the control sample is an indication that the breast cancer has metastasized or is likely to metastasize.

**22.** The method of claim **21**, wherein the assessment is indicative of whether the patient is afflicted with metastatic breast cancer that has metastasized to lymph nodes, or is likely to metastasize to lymph nodes.

**23.** A method for predicting the clinical outcome of a breast cancer patient, the method comprising:

- a) determining the level of expression of a marker in a patient sample, wherein the marker is selected from the markers listed in Table 2,

- b) determining the level of expression of the marker in a sample from a control subject having a good clinical outcome; and

- c) comparing the level of expression of the marker in the patient sample and the level of expression of the marker in the sample from the control subject;

wherein a higher level of expression of the marker in the patient sample as compared to the level of expression of the marker in the sample from the control subject is an indication that the patient has a poor clinical outcome.

**24.** A method for monitoring the progression of breast cancer in a patient, the method comprising:

- a) determining the level of expression of a marker in a patient sample from a first point in time, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2;

- b) determining the level of expression of the marker in a sample from the patient at a subsequent point in time; and

- c) comparing the level of expression detected in steps a) and b), thereby monitoring the progression of breast cancer in the patient,

wherein a change in the level of expression of the marker is indicative of either progression or regression of breast cancer.

**25.** The method of claim **24**, wherein the patient has undergone surgery to remove a tumor between the first point in time and the subsequent point in time.

**26.** The method of claim **24**, wherein the first and second samples are portions of a single sample obtained from the patient, or portions of pooled samples obtained from the patient.

**27.** A method of assessing the efficacy of a therapy for inhibiting breast cancer in a patient, the method comprising:

- a) determining the level of expression of a marker in a first sample obtained from the patient prior to administering at least a portion of the therapy to the patient, wherein the marker is selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2,

- b) determining the level of expression of the marker in a second sample obtained from the patient subsequent to administering the portion of the therapy;

- c) comparing the level of expression of the marker in the first sample as compared to the level of expression of the marker in the second sample; and

- d) determining that the therapy is efficacious for inhibiting breast cancer in the patient when there is a lower level of expression of the marker in the second sample, relative to the first sample.

**28.** A kit for assessing whether a patient is afflicted with breast cancer, the kit comprising reagents for assessing expression at least one marker selected from the group consisting of the markers listed in Table 1 and the markers listed in Table 2.

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