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(54) **CFTR WITH A PARTIALLY DELETED R DOMAIN AND USES THEREOF**

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(52) **U.S. Cl.** **536/23.5**; 530/23.1; 530/24.2; 435/69.1; 435/320.1; 435/252.3; 435/325; 435/235.1

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention offers new therapies for treating Cystic Fibrosis (CF), that are based on novel DNA molecules and proteins encoded by the DNA molecules. The present invention features DNA molecules encoding CFTR having a partially deleted R domain. The partial deletions in the R domain are between residues 708 and 835 of the wild-type CFTR.

5 Claims, 6 Drawing Sheets
(1 of 6 Drawing Sheet(s) Filed in Color)

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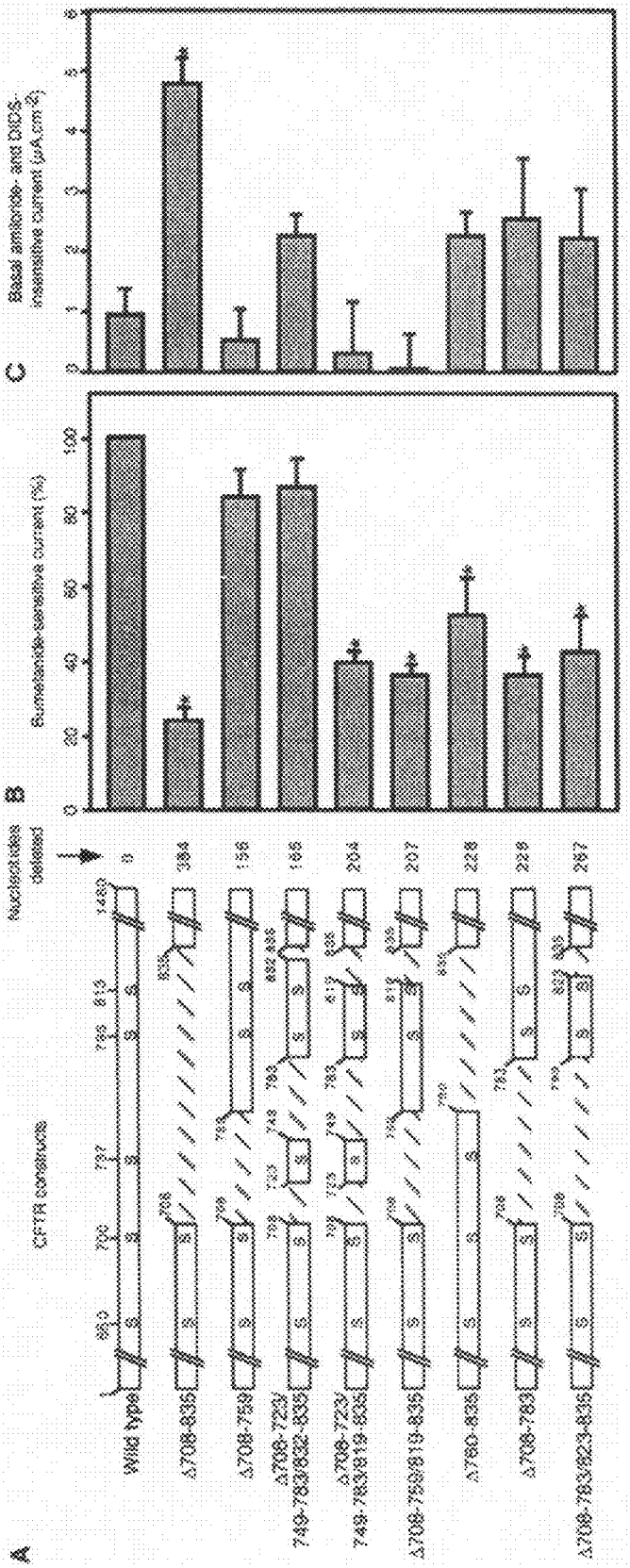
A
CFTR constructs
Wild type
Δ708-835
Δ708-759
Δ708-729
749-783/832-835
Δ708-729
749-783/819-835
Δ708-750/819-835
Δ760-835
Δ708-760
Δ708-783/823-835
Nucleotides deleted
B
Sumatriptan sensitive current (%)
C
Basal amiloride- and DIDS-insensitive current (μA.cm⁻²)

Figure 1

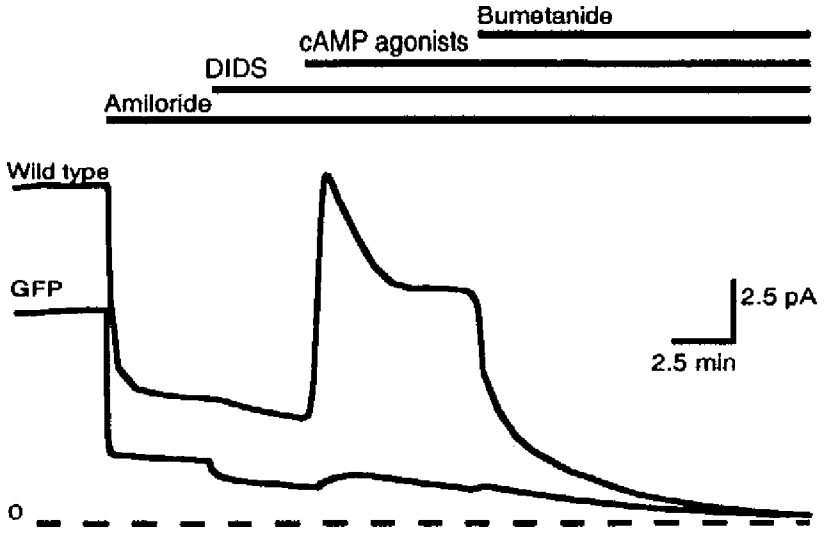
Bumetanide
cAMP agonists
DIDS
Amiloride
Wild type
GFP
2.5 pA
2.5 min
0

Figure 2

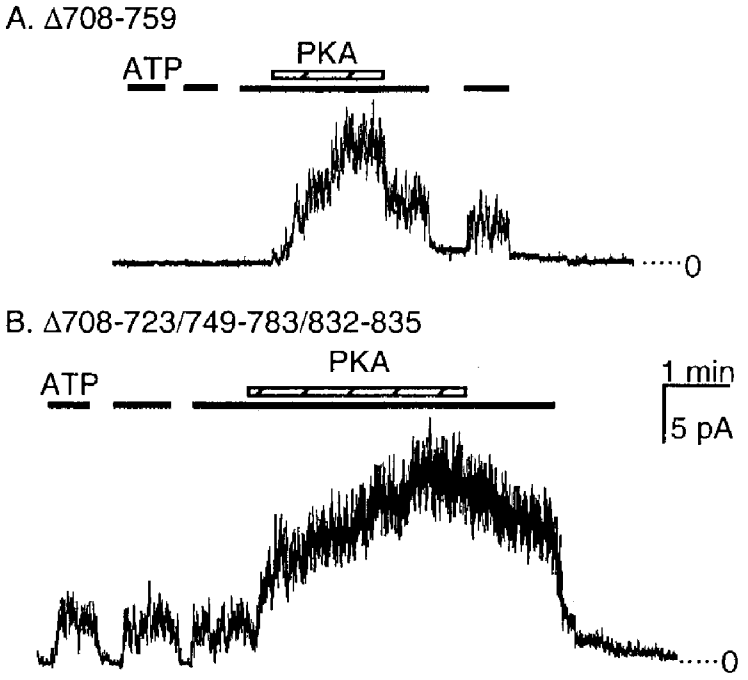

Figure 3

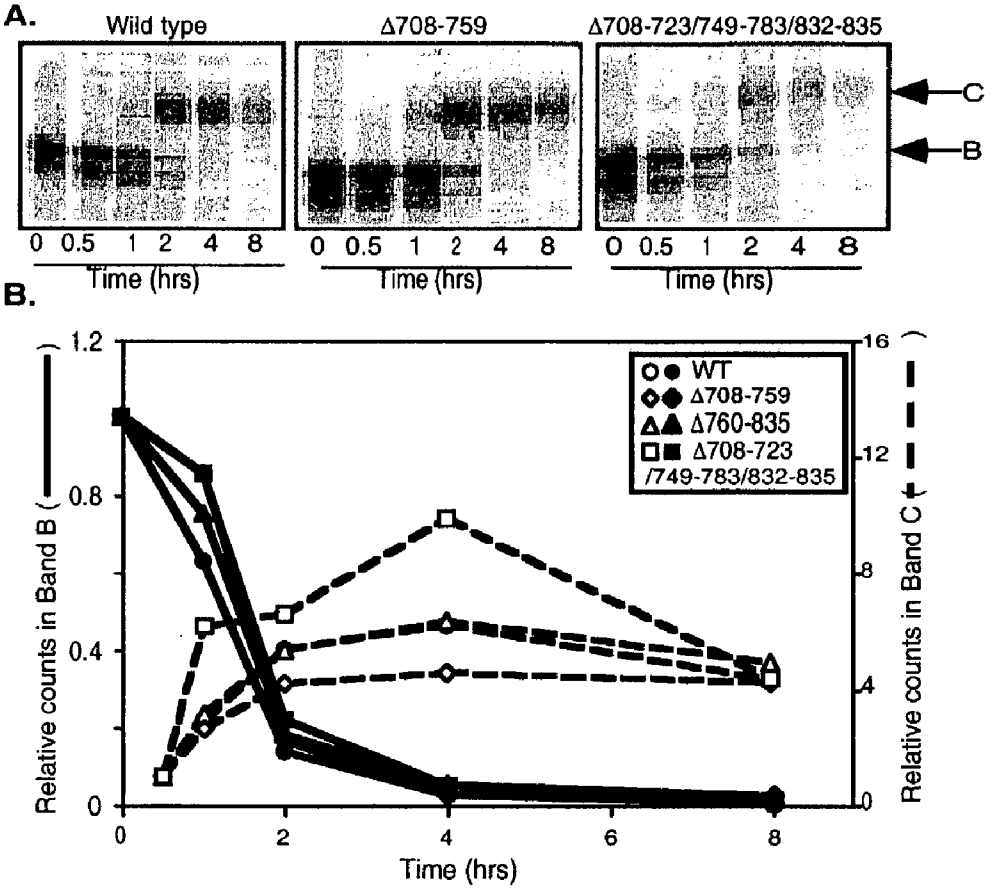
A.
Wild type
Δ708-759
Δ708-723/749-783/832-835
C
B
0 0.5 1 2 4 8
Time (hrs)
B.
WT
Δ708-759
Δ760-835
Δ708-723
/749-783/832-835
Relative counts in Band B
Relative counts in Band C
Time (hrs)

Figure 4

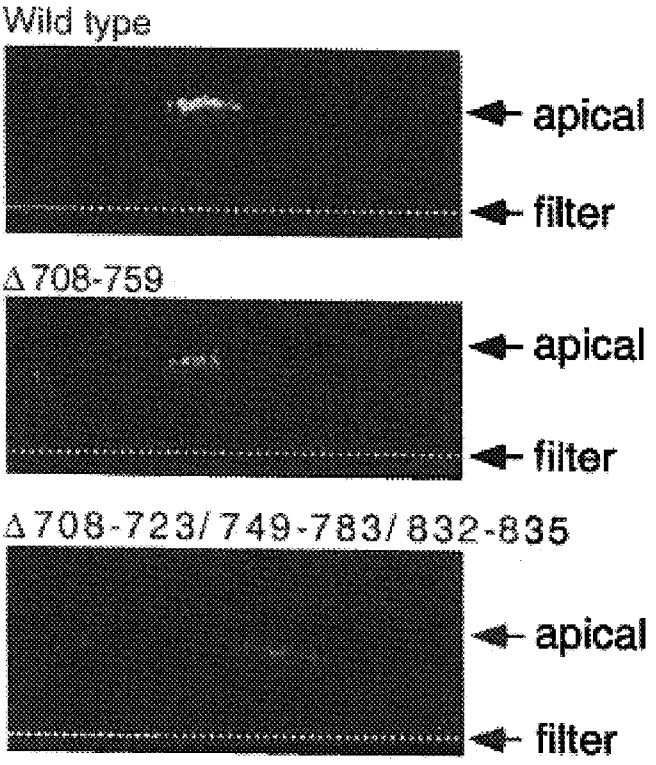
Wild type
apical
filter
Δ708-759
apical
filter
Δ708-723/749-783/832-835
apical
filter

Figure 5

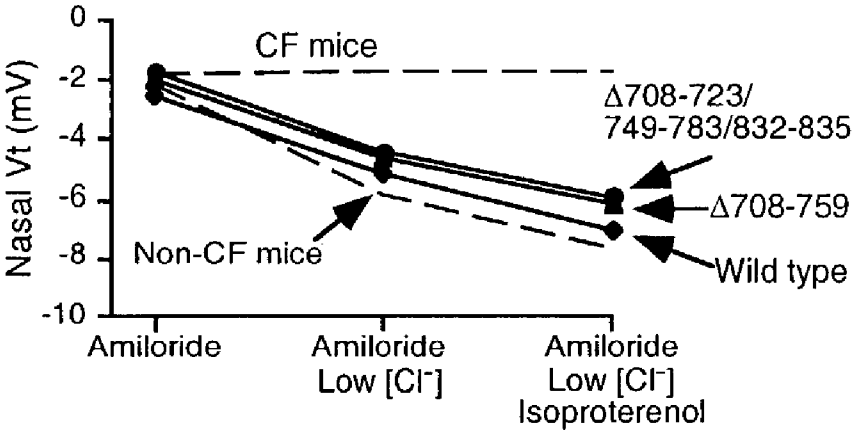
0
-2
-4
-6
-8
-10
Nasal Vt (mV)
CF mice
Δ708-723/
749-783/832-835
Δ708-759
Non-CF mice
Wild type
Amiloride
Amiloride
Low [Cl⁻]
Amiloride
Low [Cl⁻]
Isoproterenol

Figure 6

CFTR WITH A PARTIALLY DELETED R DOMAIN AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to Provisional Application No. 60/358,074, which was filed on Feb. 19, 2002.

SPECIFICATION

This invention was made in part with government support from the National Heart, Lung and Blood Institute (NHBLI). Therefore, the United States Government has certain rights in the invention.

FIELD OF THE INVENTION

This invention relates to DNA molecules encoding partially deleted CFTR and the CFTR proteins encoded thereby which are useful for treating cystic fibrosis (CF) airway disease.

BACKGROUND OF THE INVENTION

Various attempts have been made develop gene therapy for cystic fibrosis (CF) airway disease.

Airway disease is the major cause of morbidity and mortality in cystic fibrosis (CF), an autosomal recessive disease caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel. Welsh et al., *The Metabolic and Molecular Basisof Inherited Disease*, eds. Scriver, C. R., Beaudet, A. L., Sly, W. S., Valle, D., Childs, B. & Vogelstein, B. (McGraw-Hill, New York). Gene transfer offers the potential for a new and effective treatment for CF airway disease. For reviews see Davies, Geddes & Alton, 2001, *J. Gene Med.* 3:409-417; Flotte, 1999, *Curr. Opin Mol. Ther.* 1:510-516; and Welsh, 1999, *J. Clin. Invest.* 104:1165-1166. Previous studies have shown the feasibility of transferring the CFTR cDNA to CF airway epithelial cells in vitro and in vivo. However, with most vectors two main problems limit gene transfer: gene transfer from the apical surface of differentiated airway epithelia is inefficient, and DNA molecule expression is transient. See Davies, Geddes & Alton, 2001, *J. Gene Med.* 3:409-417; Flotte, 1999, *Curr. Opin Mol. Ther.* 1:510-516; and Welsh, 1999, *J. Clin. Invest.* 104:1165-1166.

For developing CF gene therapy, adeno-associated virus (AAV) vectors have several potential advantages.

One limitation of AAV vectors is the small size of a DNA molecule that can be inserted. Studies testing the insert size suggest that 4100-4900 bp is the optimal genome size for packaging. See Dong, Fran & Frizzell, 1996, *Hum Gene Ther.* 7:2101-2112. In comparison, the coding sequence of full length CFTR is 4450 bp. Riordan et al., 1989, *Science* 245:1066-1073. Addition of the two inverted terminal repeats of AAV (300 bp), and minimal 3' and 5' untranslated regions (~100 bp) yields an insert (4850 bp) that leaves little room for promoter-enhancer elements, most of which are >600 bp. Some studies have attempted to circumvent this limitation by using AAV sequences as a promoter. See Zhang et al., 1998, *Proc. Natl. Acad. Sci.* 95:10158-10163; and Flotte et al., 1993, *J. Biol. Chem.* 268:3781-3790. However, their utility in differentiated airway epithelia and in vivo is uncertain.

A potential solution to this problem is to shorten the DNA molecule by selectively deleting coding sequence. This strategy has been proposed with a mini-dystrophin gene for Duschennes muscular dystrophy (Phelps et al., 1995, *Hum. Mol. Genet.* 4:1251-1258) and for CFTR (Zhang et al., 1998, *Proc. Natl. Acad. Sci.* 95:10158-10163; and Flotte et al., 1993, *J. Biol. Chem.* 268:3781-3790).

The CFTR R (regulatory) domain (for reviews on the R domain see Ostedgaard, Baldursson & Welsh, 2001, *J. Biol. Chem.* 276:7689-7692; Sheppard & Welsh, 1999, *Physiol. Rev.* 79:S23-S45; Gadsby & Nairn, 1999, *Pysiol. Rev.* 79:S77-S107; and Ma, 2000, *News Physiol. Sci.* 15:154-158) has been speculated to be an important domain. Earlier studies in heterologous cells indicated that the CFTR R domain is predominantly random coil and that parts of the R domain can be deleted without abolishing channel function. Phosphorylation of the R domain by the cAMP-dependent protein kinase (PKA) controls CFTR Cl^- channel activity. Although this domain contains several conserved serines that are phosphorylated by PKA, no one phosphoserine is required and several different phosphoserines contribute to regulation. While the boundaries of the R domain are not precisely defined, they extend approximately from residues 634-708 at the N-terminus to approximately 835 at the C-terminus. See Ostedgaard, Baldursson & Welsh, 2001, *J. Biol. Chem.* 276:7689-7692; Ostedgaard, et al., 2000, *Proc. Natl. Acad. Sci. U.S.A.* 97:5657-5662; and Csandy et al., 2000, *J. Gen. Physiol.* 116:477-500. Previous work has shown that residues 708-831 regulate activity, but in solution they are predominantly random coil. Ostedgaard, et al., 2000, *Proc. Natl. Acad. Sci. U.S.A.* 97:5657-5662. These studies suggest that selective deletions might not severely disrupt structure and that retention of consensus phosphorylation sites might be sufficient for PKA-dependent regulation. Importantly, several earlier studies deleted portions of the R domain without abolishing channel function. Zhang et al., 1998, *Proc. Natl. Acad. Sci. U.S.A.* 95:10158-10163; Rich et al., 1991, *Science* 253:205-207; Rich et al., 1993, *Receptors Channels* 1:221-232; Ma et al., 1997, *J. Biol. Chem.* 272:28133-28141; Vankeerberghen et al., 1999, *Biochemistry* 38:14988-14998; and Xie et al., 2000, *Biophys. J.* 78:1293-1305.

While these earlier studies suggested that a DNA molecule with R domain deletions might be of value in gene therapy applications, some alterations induced channel activity in the absence of phosphorylation, reduced the response to PKA-dependent phosphorylation, and/or reduced net channel activity. Zhang et al., 1998, *Proc. Natl. Acad. Sci. U.S.A.* 95:10158-10163; Ostedgaard, Baldursson & Welsh, 2001, *J. Biol. Chem.*, 276:7689-7692; Rich et al., 1991, *Science* 253:205-207; Rich et al., 1993, *Receptors Channels* 1:221-232; Ma et al., 1997, *J. Biol. Chem.* 272: 28133-28141; Vankeerberghen et al., 1999, *Biochemistry* 38:14988-14998; and Xie et al., 2000, *Biophys. J.* 78:1293-1305. Moreover, previous studies have only examined CFTR expressed in heterologous cell lines and studied activity using the patch-clamp technique, planar lipid bilayers, or anion efflux. There is no information, prior to this invention, about their function in airway or other epithelia. Expression in epithelia is key in assessing their value for gene transfer because deletions could alter protein-protein interactions, targeting to the apical membrane, constitutive and stimulated activity, phosphorylation-dependent regulation, and perhaps toxicity.

The present invention solves these problems by deleting regions within the CFTR R (regulatory) domain (for reviews on the R domain see Ostedgaard, Baldursson & Welsh, 2001,

J. Biol. Chem. 276:7689-7692; Sheppard & Welsh, 1999, *Physiol. Rev.* 79:S23-S45; Gadsby & Nairn, 1999, *Pysiol. Rev.* 79:S77-S107; and Ma, 2000, *News Physiol. Sci.* 15:154-158) to provide a partially deleted CFTR capable of forming Cl^- channels in airway epithelia in vitro and in vivo.

SUMMARY OF THE INVENTION

The present invention offers new therapies for treating Cystic Fibrosis (CF), that are based on novel DNA molecules and proteins encoded by the DNA molecules. The present invention features DNA molecules encoding CFTR proteins having a partially deleted R domain. The partial deletions in the R domain are between residues 708 and 835 of the wild-type CFTR.

In a preferred embodiment, the DNA molecules of the present invention encode a CFTR comprising a partially deleted R domain which is capable of normal targeting to the apical membrane, wild-type biosynthesis, and generating transepithelial Cl^- current in CF epithelia (see Examples below). In addition, the CFTR protein comprising a partially deleted R domain corrects the Cl^- transport defect in a CF subject when expression in their nasal mucosa (see Examples below). In one aspect, the CFTR comprising a partially deleted R domain provides low constitutive Cl^- current in CFTR channels and provides a functional chloride ion channel in CF airway epithelia cells.

In a particularly preferred embodiment of the present invention, the CFTR comprising a partially deleted R domain has a deletion selected from the group consisting of Δ708-759, Δ708-723/749-783/832-835 and Δ760-835.

The CFTR comprising a partially deleted R domain may also comprise deletions in other regions as long as it maintains the ability to provide a functional chloride ion channel in CF airway epithelia cells. Additional deletions may be useful in producing a DNA molecule encoding a CFTR protein which is better accommodated by a vector and to ensure efficient packaging.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing (photograph) in color. Copies of this patent or patent application with color photograph will be provided by the office upon request and payment of the necessary fee.

The present invention may be better understood with reference to the attached figures in which

FIG. **1**A shows a graphic representation of exemplary embodiments of CFTR proteins of the present invention; **1**B shows bumetanide-sensitive short-circuit current in well-differentiated CF epithelia expressing the exemplary proteins shown in panel A; **1**C shows basal current;

FIG. **2** shows an example of short-circuit current in well-differentiated airway epithelia expressing wild type CFTR and GFP;

FIG. **3** shows the current from inside-out patches of membrane containing multiple CFTR channels in the presence of 1 mM ATP and PKA. **3** A is Δ708-759, and **3**B is Δ708-723/749-783/832-835;

FIG. **4**A depicts gels showing CFTR at indicated time after pulse with ^{35}S-methionine and showing the disappearance of band B (immature) and band C (mature); **4**B is a graph plotting the number of counts in band B (solid lines) and band C (dashed lines) which were determined by phosphorimaging;

FIG. **5** is an immunostaining of differentiated airway epithelia expressing exemplary embodiments of the CFTR proteins of the present invention; and

FIG. **6** shows the voltage across nasal epithelium (Vt) in CF mice expressing indicated exemplary embodiments of the CFTR proteins of the present invention in the nasal mucosa.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the surprising finding that a defective DNA molecule, namely a DNA molecule encoding a CFTR protein comprising a partially deleted R domain, expresses a protein capable of providing a functional chloride ion channel in CF epithelia cells. Based on this finding, the invention features methods for making the DNA molecules expressing CFTR protein comprising a partially deleted R domain. The DNA molecules and CFTR protein encoded thereby can be used, for example, therapeutically in CF gene and protein replacement therapies.

As used herein the following words and phrases have the meaning set forth below:

"DNA molecule" shall mean a sequence of genetic material that carries the information representing a protein.

Unless otherwise indicated, "protein" shall mean a protein, polypeptide or peptide.

"CFTR or Cystic Fibrosis Transmembrane Conductance Regulator protein" refers to a 1480 amino acid protein containing two membrane-spanning domains (MSDs), two nucleotide binding domains (NBDs) and a unique R domain, that functions as a chloride channel regulated by phosphorylation and by nucleoside triphosphates.

The phrase "cystic fibrosis transmembrane conductance regulator (CFTR) activity or function"—is meant to refer to functions normally performed by wild-type CFTR. Such functions can include mediation of ion, (e.g. chloride ion) transport across cellular membranes.

A "Cystic Fibrosis (CF) cell" is a cell that lacks cystic fibrosis transmembrane conductance regulator function. Examples include CFTR mutants of which over 1000 different varieties have been identified to date (see for example, <HTTP://genet.sickkids.on.ca>).

"R (regulator) domain" refers to a domain that keeps a chloride channel closed at rest and which opens the channel when phosphorylated (e.g. by cAMP-dependent protein kinase (PKA) or protein kinase C (PKC)). The R domain of CFTR is encoded by a portion of exon 13, and generally comprises 128 amino acid residues that span from about amino acid residues 708 to 835 of full length CFTR or a lesser portion within this stretch. Ostedgaard et al., 2000, *Proc. Natl. Acad. Sci. USA* 97:5657-5662.

"Partially deleted R domain" refers to deletion of part, but not all, of the R domain.

"CF gene therapy" refers to the transfer of genetic material (e.g., DNA or RNA) encoding CFTR functional activity into a host to treat or prevent Cystic Fibrosis (CF).

"CF protein replacement therapy" refers to transfer of a protein having CFTR functional activity into a host to treat or prevent CF.

The nucleotide and amino acid sequence for full-length CFTR and modifications encoding CF mutant are known in the art (See, e.g., European Patent No. 0446017). Based on this information, one of skill in the art can obtain DNA molecules encoding CFTR comprising a partially deleted R domain using techniques that are well-known. For example, DNA molecules encoding CFTR can be isolated from appro-

priate cells or plasmids using standard techniques (e.g. restriction enzyme cleavage). Genetic material encoding full-length CFTR can then be modified (e.g. via deletion mutagenesis using Quik Change™ Mutagenesis, Stratagene, La Jolla, Calif.) to obtain a DNA molecule encoding a CFTR comprising a partially deleted R domain. Alternatively, a DNA molecule encoding a CFTR protein comprising a partially deleted R domain can be generated synthetically using standard modes of polynucleotide synthesis. A candidate gene can be tested to determine whether it in fact encodes functional CFTR activity, for example, using the techniques detailed below in the Examples.

An "expression cassette" comprising the gene encoding a CFTR comprising a partially deleted R domain operably linked or under the control of transcriptional and translational regulatory elements (e.g. a promoter, ribosome binding site, operator or enhancer) can be made and used for expression of CFTR protein comprising a partially deleted R domain in vitro or in vivo. The choice of regulatory elements employed may vary, depending, for example, on the host cell to be transfected and the desired level of expression. Several promoters for use in mammalian cells are known in the art and include, inter alia, the phosphoglycerate (PGK) promoter, the simian virus 40 (SV40) early promoter, the Rous sarcoma virus (RSV) promoter, the adenovirus major later promoter (MLP) and the human cytomegalovirus (CMV) immediate early 1 promoter. However, any promoter that facilitates suitable expression levels can be used in the present invention. Inducible promoters (e.g., those obtained from the heat shock gene, metallothionene gene, beta interferon gene, or steroid hormone responsive genes) may be useful for regulating transcription based on external stimuli.

A preferred DNA molecule encodes a CFTR protein comprising a deletion in the R domain wherein the deletion is selected from the group consisting of Δ708-835 (SEQ ID NO:1), Δ708-759 (SEQ ID NO:2), Δ708-723/749-783//832-835 (SEQ ID NO:3), Δ708-723/749-783/819-835 (SEQ ID NO:4), Δ708-759/819-835 (SEQ ID NO:5), Δ760-835 (SEQ ID NO:6), Δ708-783 (SEQ ID NO:7), and Δ708-783/823-835 (SEQ ID NO:8). A preferred CFTR protein comprises a deletion in the R domain wherein the deletion is selected from the group consisting of Δ708-835 (SEQ ID NO:9), Δ708-759 (SEQ ID NO:10), Δ708-723/749-783//832-835 (SEQ ID NO:11), Δ708-723/749-783/819-835 (SEQ ID NO:12), Δ708-759/819-835 (SEQ ID NO:13), Δ760-835 (SEQ ID NO:14), Δ708-783 (SEQ ID NO:15), and Δ708-783/823-835 (SEQ ID NO:16). More preferably, the DNA molecule encodes a CFTR protein comprising a deletion in the R domain selected from the group consisting of Δ708-759 (SEQ ID NO:2), Δ708-723/749-783//832-835 (SEQ ID NO:3), and Δ760-835 (SEQ ID NO:6) and the CFTR protein comprises a deletion in the R domain selected from the group consisting of Δ708-759 (SEQ ID NO:10), Δ708-723/749-783//832-835 (SEQ ID NO:11), and Δ760-835 (SEQ ID NO:14). In a particularly preferred embodiment, the DNA molecule encodes a CFTR protein comprising a deletion in the R domain of a of Δ708-759 (SEQ ID NO:2) and the CFTR protein comprises a deletion in the R domain Δ708-759 (SEQ ID NO:10). The CFTR protein of the present invention which comprises a deletion in the R domain is capable of providing a functional chloride ion channel in CF airway epithelia cells.

The DNA molecule of the present invention, and the protein encoded thereby may further comprise deletions of other regions of CFTR provided that the resultant CFTR protein is capable of providing a functional chloride ion channel in CF airway epithelia cells.

In another aspect of the invention, there is provided a DNA molecule encoding a CFTR protein comprising a partially deleted R domain wherein the encoded CFTR has low constitutive Cl^- current. As used herein, "low constitutive Cl^- current" means an amount of Cl^- current as determined in patch-clamp studies (described by Baldursson et. al., 2001, *J. Biol. Chem.* 276:1904-1910) which is less than 2 $\mu A.cm^{-2}$. In one embodiment, the CFTR having low constitutive Cl^- current is selected from the group consisting of SEQ ID NO:10, SEQ ID NO:12, and SEQ ID NO:13. The corresponding DNA molecule is selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:5.

The CFTR proteins of the present invention which comprise a partially deleted R domain can be made by introducing the DNA molecules of the present invention into cells in culture using standard techniques (e.g. via calcium phosphate or calcium chloride co-precipitation, or via infection with a recombinant virus, such as a recombinant adenovirus, comprising the DNA molecule, DEAE dextran mediated transfection, lipofection, or electroporation). Recombinant cells can then be cultured in vitro in a manner that allows expression of the CFTR proteins of the present invention. Preferred host cells for generating the CFTR proteins of the present invention include, inter alia, mammalian cells, such as HeLa cells, COS cells, C127 cells; yeast cells, insect cells and bacterial cells.

The CFTR proteins of the present invention which comprise partially deleted R domains can be purified from host cell membranes using known methods, such as ion exchange chromatography, gel filtration chromatography, electrophoresis and affinity chromatography. (Tilly et. al., 1992, *The Journal of Biological Chemistry* 2679470-73). A preferred method of purification involves first solubilizing the protein in the presence of a nondenaturing detergent.

The CFTR proteins of the present invention comprising partially deleted R domains produced as described herein can be used, for example, in protein replacement therapies and the DNA molecule in gene therapies for Cystic Fibrosis as described in detail below.

Protein therapy may be accomplished by any method that effectively introduces the CFTR protein of the present invention into the membrane of CF defective cells to imbue on those cells CFTR activity. An effective amount of a CFTR protein of the present invention comprising a partially deleted R domain (i.e. an amount sufficient to reduce or eliminate the symptoms associated with CF and/or to provide a functional chloride ion channel in CF airway epithelia cells) can be administered alone or in association with an agent that facilitates passage (e.g. via fusion or endocytosis) through cell membranes to CF patients (i.e. patients having CF defective cells). The "effective amount" can be determined by one of skill in the art based on such factors as the type and severity of symptoms being treated, the weight and/or age of the subject, the previous medical history of the subject, and the selected route for administration of the agent.

Preferably for use in protein therapy, the CFTR proteins comprising partially deleted R domains are associated with lipids, such as detergents or other amphipathic molecule micelles, membrane vesicles, liposomes, virosomes, or microsomes. Lipid compositions that are naturally fusogenic or can be engineered to become fusogenic (e.g. by incorporating a fusion protein into the lipid) are especially preferred. Fusion proteins can be obtained from viruses such as parainfluenza viruses 1-3, respiratory syncytial virus (RSV), influenza A, Sendai virus, and togavirus fusion protein. Nonviral

fusion proteins include normal cellular proteins that mediate cell-cell fusion. Other nonviral fusion proteins include the sperm protein PH-30 which is an integral membrane protein located on the surface of sperm cells that is believed to mediate fusion between the sperm and the egg. See Blobel et al., 1992, *Nature* 356:248-251. Still other nonviral fusion proteins include chimeric PH-30 proteins such as PH-30 and the binding component of hemaglutinin from influenza virus and PH-30 and a disintegrin (e.g. bitistatin, barbourin, kistrin, and echistatin). In addition, lipid membranes can be fused using traditional chemical fusogens such as polyethylene glycol (PEG).

A CF patient can be treated by administration of an effective amount of a CFTR protein comprising a partially deleted R domain, optionally in a pharmaceutically acceptable carrier or diluent. An effective amount of a CFTR protein comprising a partially deleted R domain is an amount sufficient alleviate the symptoms of CF and/or an amount to provide a functional chloride ion channel in CF airway epithelia cells. A CFTR protein comprising a partially deleted R domain can be administered subcutaneously, intravenously, intraperitoneally, intramuscularly, parenterally, orally, submucosally, by inhalation, or other appropriate route of administration in an effective dosage range. A preferred route of administration is by inhalation (e.g. of an aerosolized pharmaceutical composition). If necessitated by a particular mode of administration, CFTR proteins comprising partially deleted R domains can be encapsulated within a material that protects it from enzymatic degradation. In addition, prior to administration, it may be useful to administer agents to clear mucus (e.g. using a DNAse) and/or bacterial infection.

Alternatively, a preparation of the gene encoding a CFTR protein comprising a partially deleted R domain can be incorporated into a suitable vector for delivering the gene into a CF patient's defective cells. As many of the symptoms of CF manifest themselves in the respiratory tract, the preparation can be delivered directly to the airways of CF patients.

The first generation of CF gene therapy may be transient and may require repeated delivery to the airways. Eventually, however, gene therapy may offer a cure for CF when the identity of the precursor or stem cell to air epithelial cells becomes known. If genetic material encoding CFTR proteins comprising partially deleted R domains were incorporated into airway stem cells, all subsequent generations of such cells would make authentic CFTR protein comprising a partially deleted R domain from the integrated sequences and would correct the physiological defect almost irrespective of the biochemical basis of the action of CFTR.

For use in treating CF, appropriate vectors must: 1) effectively infect lung epithelia or other tissue manifesting the disease and deliver the therapeutic nucleic acid encoding CFTR function; 2) be appropriately maintained in host cells; and 3) be safe. The following describes a number of approaches and vectors that may prove useful for performing CF gene therapy. The following listing, however, is not intended to be exhaustive and many other vectors should prove useful for performing gene therapy with the novel genes disclosed herein.

Retroviruses—Although defective retroviruses are one of the best characterized system (Miller, A. D., 1990, *Blood* 76:271), the major issue in relation to CF is the requirement for dividing cells to achieve DNA integration and gene expression. Were conditions found to induce airway cell division, the in vivo application of retroviruses, especially if repeated over many years, would necessitate assessment of the safety aspects of insertional mutagenesis in this context.

Adeno-Associated Virus—(AAV) is a naturally occurring defective virus that requires other viruses such as adenoviruses or herpes viruses as helper viruses (Muzyczka, N., 1992, *Current Topics in Microbiology and Immunology* 158:97). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. AAV vectors therefore may prove useful for expressing genes encoding the CFTR proteins of the present invention comprising partially deleted R domains, although genes encoding fall length CFTR approach AAV's upper limit. For reviews see Flotte, 1999, *Curr. Opin. Mol. Ther.* 1:510-516; Carter & Samulski, 2000, *Int. J. Mol. Med.* 6:17-27; and Athanasopoulos & Dickson, 2000, *Int. J. Mol. Med* 6:363-375. AAV has already been successfully used to produce Factor IX in humans with hemophilia B. In AAV vectors, viral genes are deleted, thereby minimizing cell-mediated immune responses. AAV vectors can transduce non-dividing cells, such as airway epithelia. And DNA molecule expression can be prolonged. Although, most previous studies have used type 2 AAV vectors, its receptor is on the basolateral membrane and thus inaccessible to vector applied apically. See, Summerford & Samulski, 1998, *J. Virol.* 72:1438-1445. Recent studies have discovered that type 5 AAV can efficiently transduce well-differentiated human airway epithelia, and that its receptor lies on the apical membrane. See Zabner et al., 2000, *J. Virol.* 74:3852-3858; Walters et al. 276:20610-20616 Type 6 AAV is also a promising vector for airway epithelia. See Halbert, Allen & Miller, 2001, *J. Virol.* 75:6615-6624.

Naked DNA—Naked plasmid can be introduced into muscle cells by injection into the tissue. Expression can extend over many months but the number of positive cells is low (Wolff, J. et al., 1989, *Science* 247:1465).

DNA-Lipid Complexes—Lipid carriers can be associated with naked DNA (e.g. plasmid DNA) to facilitate passage through cellular membranes. Cationic, anionic, or neutral lipids can be used for this purpose. However, cationic lipids are preferred because they associate better with DNA, which generally has a net negative charge. Cationic lipids have been shown to mediate intracellular delivery of plasmid DNA (Felgner, P. and Ringold, G. M., 1989, *Nature* 337:387). Injection of cationic lipid plasmid DNA complexes into the circulation of mice has been shown to result in expression of the DNA in lung (Brigham, K. et al., 1989, *Am. J. Med. Sci.* 298:278). Instillation of cationic lipid plasmid DNA into lung has also been found to be expressed in epithelial cells but the efficiency of expression has been reported as being relatively low and transient (Hazinski, T. A. et al., 1991, *Am. J Respir., Cell Mol. Biol.* 4:206).

Receptor Mediated Entry—In an effort to improve the efficiency of plasmid DNA uptake, attempts have been made to utilize receptor-mediated endocytosis as an entry mechanisms and to protect DNA in complexes with polylysine (Wu, G. and Wu, C. H., 1988, *J. Biol. Chem.* 263:14621). One potential problem with this approach is that the incoming plasmid DNA enters the pathway leading from endosome to lysosome, where much incoming material is degraded. One solution to this problem is the use of transferrin DNA-polylysine complexes linked to adenovirus capsids (Curiel, D. T. et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8850). The latter enter efficiently but have the added advantage of naturally disrupting the endosome thereby avoiding shuttling to the lysosome.

Adenovirus—Defective adenoviruses may also be useful for CF gene therapy (Berkner, K. L., 1988, *BioTechniques* 6:616). Adenovirus can be manipulated such that it encodes and expresses the desired gene product, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. In addition, adenovirus has a natural tropism for airway epithelia. The viruses are able to infect quiescent cells as are found in the airways, offering a major advantage over retroviruses. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al., 1974, *Am. Rev. Respir. Dis.* 109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al., 1991, *Science* 252:431-434; Rosenfeld et al., 1992, *Cell* 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al., 1979, *Proc. Natl. Acad. Sci. USA* 76:6606).

A first generation adenovirus encoding full length CFTR has been prepared and includes viral DNA derived from the common relatively benign adenovirus 2 serotype. A similar vector can be prepared to express CFTR proteins comprising partially deleted R domains. The E1a and E1b regions of the viral genome, which are involved in early stages of viral replication have been deleted. Their removal impairs viral gene expression and viral replication. The protein products of these genes also have immortalizing and transforming function in some non-permissive cells.

The following properties would be desirable in the design of a viral vector to transfer the gene for a CFTR protein comprising a partially deleted R domain to the airway cells of a CF patient. The vector should allow sufficient expression of the CFTR protein, while producing minimal viral gene expression. There should be minimal viral DNA replication and ideally no virus replication. Finally, recombination to produce new viral sequences and complementation to allow growth of the defective virus in the patient should be minimized.

The present invention is further illustrated by the following examples which in no way should be construed as being further limiting.

EXAMPLES

Example 1

Construction of CFTR Variants

DNA molecules encoding exemplary embodiments of CFTR proteins comprising partial deletions in the R domain were made in pTM1-CFTR4 by PCR deletion mutagenesis (Quik Change Mutagenesis™, Stratagene, La Jolla, Calif.) and confirmed by sequencing. Constructs were ligated into an adenovirus serotype 5 vector in which the CMV promoter drives cDNA expression. The exemplary CFTR proteins were named by the residues that were deleted; for example in Δ708-835, residues between and including aa 708 and 835 are deleted. An identical adenovirus expressing green fluorescent protein (GFP) was used as a negative control. FIG. **1**A shows the eight variants constructed which include, Δ708-835 (SEQ ID NO:9), Δ708-759 (SEQ ID NO:10), Δ708-723/749-783/832-835 (SEQ ID NO:11), Δ708-723/749-783/819-835 (SEQ ID NO:12), Δ708-759/819-835 (SEQ ID NO:13), Δ760-835 (SEQ ID NO:14), Δ708-783 (SEQ ID NO:15), and Δ708-783/823-835 (SEQ ID NO:16). FIG. **1**A indicates the deletions by crosshatching. Serines that are phosphorylated in vivo are indicated in FIG. **1**A with residue number at the top. First and last residue of deleted regions are indicated above each construct. The number of nucleotides deleted in each variant is shown on the right of FIG. **1**A.

Example 2

Protein Biochemistry

To confirm protein size and phosphorylation, HeLa cells were infected with 200 MOI of recombinant adenovirus in Eagles minimal essential media (EMEM) for 45 min. Cells were lysed 18-24 hr later, CFTR immunoprecipitated, and phosphorylated with γ-^{32}P-ATP and the catalytic subunit of PKA as described previously. Baldursson et al., 2001, *J. Biol. Chem.* 276:1904-1910. For pulse chase studies, HeLa cells were infected as above, and after 18-24 hr cells were methionine starved, labeled with ^{35}S-methionine, and pulse-chase studies carried out as described previously (Ostedgaard, Zeiher & Welsh, 1999, *J. Cell Sci.* 112:2091-2098. Proteins were separated on 8% SDS-PAGE, stained, destained, dried and exposed to phosphorscreens. After phosphorimaging, counts in bands B (immature) and C (mature) were quantitated. FIGS. **4**A&B show that two representative CFTR proteins of the present invention comprising partially deleted R domains, namely Δ708-759 and Δ708-723/749-783/832-835, demonstrate similar disappearance of band B and appearance of band C as wild type. FIG. **4**A shows the appearance in a gel and FIG. **4**B is the quantitation of the bands from 3-4 experiments. Band B is shown as counts relative to counts at time=0; band C is shown as counts relative to counts at time=0.5 hr. (n=3-4 for all points.)

Example 3

Well-differentiated CF Airway Epithelia

Cultures of human airway epithelia were obtained from CF bronchus (ΔF508/ΔF508 or ΔF508/other genotypes) and cultured at the air-liquid interface as previously described (Karp et al., 2002, *Epithelial Cell Culture Protocols*, ed. Wice (Human, Totowa, N.J.) 188:115-137, incorporated herein by reference. Epithelia were used at least 14 days after seeding when they were well-differentiated with a surface consisting of ciliated cells, goblet cells and other non-ciliated cells. They also retained the functional properties of airway epithelia including transepithelial electrolyte transport and resistance. FIG. **2** shows the short circuit current in well-differentiated airway epithelia in the presence of wild-type CFTR and GFP, demonstrating that wild-type CFTR can provide a functional chloride ion channel in CF airway epithelia. Bars at top of FIG. **2** indicate additions to solutions (detailed below in Example 5). Zero current level is shown by dashed line.

Epithelia were infected with 200 MOI adenovirus vector using 5 mM EGTA applied to the apical surface to transiently disrupt the tight junctions as previously described (Walters et al., 1999, *J. Biol. Chem.* 274:10219-10226.

Example 4

Immunocytochemistry

Three days following gene transfer, epithelia were fixed with 4% paraformaldehyde, permeabilized with 0.2% Triton X-100, blocked with 5% normal goat serum in SuperBlock (Pierce, Rockford, Ill.), and stained with anti-CFTR (24-1, R&D Systems, Minneapolis, Minn.) and anti-ezrin primary antibodies. Appropriate Alexa Fluor-conjugated secondary antibodies were then applied and epithelia were examined by confocal laser scanning microscopy. FIG. **5** shows X-Z confocal image reconstructions.

Example 5

Ussing Chamber Studies

Three days following gene transfer, short-circuit current was measured in symmetrical solutions containing: 135 mM NaCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, 2.4 mM K_2PO_4, 0.6 mM KH_2PO_4, 5 mM dextrose and 5 mM Hepes, pH 7.4, as previously described (Zabner et al., 1998, *Mol. Cell* 2:397-403. After measuring baseline current, mucosal amiloride (10^{-4} M), mucosal 4,4'-diisothiocyanoto-stilbene-2,2'-disulfonic acid (DIDS, 10^{-4} M); the cAMP agonists mucosal forskolin (10^{-5} M) plus 3-isobutyl-2-methylxanthine (IBMX, 10^{-4} M), and submucosal bumetanide (10^{-4} M) were sequentially added (see FIG. **2**). For a limited number of studies, epithelia were treated with forskolin (10^{-5} M) and IBMX (10^{-4} M) for 24 hr prior to study in Ussing chambers to minimize basal CFTR current.

Example 6

Patch-clamp Studies

The methods, solutions, and procedures for excised, inside-out patch-clamp recording were identical to those previously described (Carson, Travis & Welsh, 1995, *J. Biol. Chem.* 270:1711-1717). Patches containing multiple CFTR channels were studied at room temperature (~24° C.) in the presence of 1 mM ATP±75 nM PKA added to the bath solution. Membrane voltage was clamped at −40 mV; data were filtered at 100 Hz and digitized at 250 Hz.

Example 7

Nasal Voltage Study in CF Mice

For in vivo analysis, we used 6-8 wk old ΔF508 homozygote CF mice (Zeiher et al., 1995, *J. Clin. Invest.* 962051-2064. Mice were lightly anesthetized in a halothane chamber. Adenovirus vectors (5×10^9 particles) were administered intranasally as Ad:CaPi coprecipitates (Fasbender et al., 1998, *J. Clin. Invest.* 102:184-193) in two 5 μl instillations delivered 5 min apart. Four days later animals were anesthetized with ketamine and xylazine and the transepithelial electric potential difference across the nasal epithelium (Vt) was measured as previously described (Zeiher et al., 1995, *J. Clin. Invest.* 96:2051-2064). During measurement of Vt, the nasal mucosa was perfused at a rate of 50 μl/min with a Ringer's containing (in mM) 135 NaCl, 2.4 KH_2PO_4, 0.6 K_2HPO_4, 1.2 $CaCl_2$, 1.2 $MgCl_2$, and 10 HEPES (pH 7.4 with NaOH). Three solutions were used: a) Ringer's containing 100 μM amiloride; b) Ringer's containing 135 mM Na-gluconate substituted for NaCl plus amiloride; and c) Na-gluconate Ringer's containing 10 μM isoproterenol and amiloride. Measurements were made after perfusion for 5 min.

Example 8

Results

A. Generation of CFTR with R Domain Deletions

Portions of the R domain were selectively deleted based on known PKA motifs and earlier structure and function studies (Ostedgaard, Baldursson, & Welsh, 2001, *J. Biol. Chem.* 276:7689-7692; Sheppard & Welsh, 1999, *Physiol. Rev.* 79:S23-S45; and Gadsby & Nairn, 1999, *Physiol Rev.* 79:S77-S107). Because previous work showed that residues 708-835 are the largest deletion that yields a functional channel in mammalian cells (Rich et al., 1993, *Receptors Channels* 1:221-232), deletions were made in this region. In addition, constructs were produced that retained different numbers of the phosphoserines. FIG. **1**A shows the deletion constructs. The cDNA for each variant was inserted into a recombinant adenovirus vector. Infection of HeLa cells produced approximately equivalent amounts of protein of the predicted size; it was recognized by CFTR antibodies and was phosphorylated in vitro by the catalytic subunit of PKA.

B. Function of R Domain Variants in Well-differentiated CF Airway Epithelia

To determine whether the R domain variants can complement the CF Cl^- transport defect, the variants were expressed in well-differentiated CF airway epithelia and the short-circuit current response to several interventions was measured. FIG. **2** shows the interventions and an example of the currents. The following were sequentially added: a) amiloride to inhibit apical Na^+ channels, hyperpolarize the apical membrane, and thereby generate a driving force for Cl^- secretory currents; b) DIDS to inhibit DIDS-sensitive apical Cl^- channels; c) cAMP agonists to activate CFTR; and d) bumetanide to inhibit basolateral Cl^- co-transport. Under these conditions, bumetanide-sensitive current provides the most accurate assessment of CFTR-dependent transepithelial Cl^- transport.

All the CFTR variants produced transepithelial Cl^- currents (FIG. **1**B). The data in FIG. **1**B represent the difference in current generated by adding bumetanide corrected for current in GFP expressing epithelia and normalized to current generated by wild type CFTR. Bumetanide-sensitive current for epithelia expressing wild type CFTR was 20.3±1.6 $\mu A.cm^{-2}$. The asterisks in FIG. **1**B indicate the value different from wild type ($p<0.05$, one way ANOVA) ($n=18$ for wild type and 6-15 for each variant).

Because the constructs in CF epithelia obtained from multiple different lungs were tested, in each culture the responses of the variants were compared to epithelia expressing GFP (as a negative control) and then normalized current to the response of wild-type CFTR. As shown in FIG. **1**B, the Δ708-835 variant generated the least Cl^- current, consistent with patch-clamp studies showing that this channel has a low open state probability ((Winter & Welsh, 1997, *Nature* 389:294-296; and Rich et al., 1993, *J. Biol. Chem.* 268:20259-20267). Two variants generated current similar to wild-type CFTR: Δ708-759 and Δ708-723/749-783/832-835 (FIG. **1**B). The other variants produced intermediate levels of Cl^- current (FIG. **1**B).

Amiloride-inhibited current has been reported to be increased in CF epithelia (Boucher, 1994, *Am J. Respir. Crit. Care Med.* 150:271-281; Schweibert et al., 1999, *Physiol.*

Rev. 79:S145-S166). However, the responsible mechanism remains uncertain and a direct effect of CFTR on the Na^+ currents has not been uniformly observed (Schweibert et al., 1999, *Physiol. Rev.* 79:S145-S166; and Nagel et al., 2001, *EMBO Rep.* 2:249-254). Prior studies showed limited and variable effects on Na^+ current. However, in the present invention, amiloride-inhibited current is influenced not only by the activity of epithelial Na^+ channels, but also by the basal Cl^- current which is increased when amiloride hyperpolarizes the apical membrane. Moreover, in the present invention, there was no control for the percentage of cells infected in different experiments. Although gene transfer to 5-10% of cells is sufficient to correct the CF Cl^- transport defect (Davies, Geddes, & Alton, 2001, *J. Gene Med.* 3:409-417; Flotte, 1999, *Curr. Opin. Mol. Ther.* 1:510-516; and Welsh, 1999, *J. Clin. Invest.* 104:1165-1166), alteration of Na^+ current may depend on the percentage of infected cells over a wide range (Johnson et al., 1995, *J. Clin. Invest* 95:1377-1382).

Patch-clamp studies in heterologous cells demonstrated that some of the CFTR proteins of the present invention comprising partially deleted R domains opened even without PKA phosphorylation; i.e., they were constitutively active (Ostedgaard, Baldursson, & Welsh, 2001, *J. Biol. Chem.* 276:7689-7692). To assess constitutive activity, epithelia were first treated with cAMP agonists for 24 hr prior to mounting them in Ussing chambers; this treatment minimizes basal CFTR Cl^- channel activity. Then the current remaining after treatment with amiloride and DIDS, but before addition of cAMP agonists was measures, as shown in FIG. **1**C, and FIG. **2**). In FIG. **1**C, the basal current was measured in the presence of amiloride and DIDS and corrected for current in epithelia expressing GFP. All epithelia were pre-treated with cAMP agonists for 24 hr. Asterisks in FIG. **1**C indicate values different from wild type ($p<0.05$, one way ANOVA) (n=3-6 for each construct).

Interestingly, Δ708-835 produced a large basal current, consistent with previous patch-clamp studies showing that it generates significant constitutive but little total Cl^- current. Wild type and the other CFTR proteins of the present invention comprising partially deleted R domains surprisingly showed low basal/constitutive current. In one embodiment of the present invention, such low basal/constitutive current is preferred.

C. Constitutive Activity of CFTR with R Domain Deletions

To test further for constitutive activity, we examined the two variants generating the largest Cl^- currents in airway epithelia by expressing them in HeLa cells and measuring activity in excised, inside-out patches. Consistent with the transepithelial studies shown in FIG. **1**C, FIG. **3** shows that Δ708-723/749-783/832-835, but not Δ708-759 generated constitutive current. Specifically, FIG. **3**A shows that Δ708-759 showed no current before phosphorylation with PKA and FIG. **3**B shows that Δ708-723/749-783/832-835 activity was stimulated with ATP alone. The ratio of current with ATP alone to the maximal current with PKA and ATP was 0.22±0.01, n=4.

D. Biosynthesis and Localization of the R Domain Variants

The glycosylation state of CFTR traces its progress through the biosynthetic pathway (Cheng et al., 1990, *Cell* 63:827-834). In the endoplasmic reticulum, CFTR appears as a partially glycosylated intermediate, band B (immature). In the Golgi complex, the protein becomes fully glycosylated, appearing as band C (mature); this is the form that traffics to the plasma membrane. A pulse-chase analysis to assess biosynthesis of the R domain variants was used. FIG. **4** shows results for wild-type CFTR and three of the CFTR proteins comprising partially deleted R domains of the present invention. The rates at which band B disappeared and band C appeared were similar for each of the CFTR proteins of the present invention and wild type.

CFTR resides in the apical membrane of non-CF epithelia where it provides a pathway for Cl^- flow (Welsh et al., 2000, *The Metabolic and Molecular Basis of Inherited Disease*, eds. Scirver, Beaudet, Sly, Valle, Childs & Vogelstein (McGraw-Hill, New York) pp 5121-5189); an apical location is critical for its function in transepithelial Cl^- transport. The exemplary embodiments of CFTR proteins comprising partially deleted R domains of the present invention were expressed in well-differentiated CF airway epithelia, immunostained CFTR, and the pattern of fluorescence using confocal microscopy was examined. All the constructs showed the same apical localization as wild type CFTR; FIG. **5** shows examples for Δ708-759 and Δ708-723/749-783/832-835. In FIG. **5**, data are X-Z confocal images. Arrows indicate the position of the apical membrane and the top of the filter support. Anti-CFTR immunostaining is green and anti-ezrin staining is red. Ezrin stains the apical region of the epithelial cells.

E. In vivo Function of R Domain Variants in the Nasal Epithelia of CF Mice

As an additional test of their combined biosynthesis, localization, and functional activity, the variants were tested in an art recognized animal model in vivo. Zeiher et al., 1995, *J. Clin. Invest.* 96:2051-2064. Nasal epithelia of CF mice were infected with adenovirus vectors expressing wild type and the two CFTR proteins of the present invention that generated the largest Cl^- current in human airway epithelia. Epithelia were treated with amiloride to inhibit Na^+ channels and then Vt in response to perfusion was measured with solutions containing a low Cl^- concentration and isoproterenol to elevate cellular cAMP levels. As shown in FIG. **6**, Expression of Δ708-759 and Δ708-723/749-783/832-835 corrected the nasal voltage defect to a similar extent as wild-type CFTR and to levels similar to those previously observed in non-CF mice (Zeiher et al., 1995, *J. Clin. Invest.* 96:2051-2064). In FIG. **6**, values of Vt obtained from untreated CF and wild type mice are indicated by dashed lines. The three interventions are indicated at the bottom of FIG. **6** (n=13 for wild type and 14 for the deleted variants).

The data show that CFTR constructs with multiple R domain deletions retain normal biosynthesis, apical targeting and Cl^- channel function when expressed in differentiated CF airway epithelia. These results have implications for developing CF gene therapy and for understanding CFTR structure and function.

The data also establish the feasibility to generate a smaller CFTR DNA molecule to accommodate the limited packaging capacity of AAV in vitro and in vivo. For optimal use in an AAV vector for CF gene therapy, the DNA molecule would have two characteristics. The DNA molecule would be short to facilitate packaging, and the protein product would correct the CF defect to the same extent as wild type CFTR.

Of these three constructs, Δ708-759 most closely resembled wild type, in that it produced no constitutive Cl^- current. In contrast, Δ708-723/749-783/832-835 and Δ708-759/819-835 had greater, but still low, basal Cl^- currents than wild type and showed constitutive Cl^- current when examined in patch-clamp studies.

Example 9

Structure of CFTR

The CFTR proteins of the present invention which comprise partially deleted R domains provide insight into CFTR structure. All the CFTR proteins comprising partially deleted R domains of the present invention were capable of targeting exclusively to the apical membrane, indicating that important apical targeting motifs are not likely located within this region of the R domain. CFTR proteins of the present invention also showed normal biosynthesis, suggesting that sequences in the deleted regions are not required for normal processing. Apical targeting and biosynthesis were also normal with and without constitutive activity, suggesting that Cl^- channel activity may not influence these processes. Other studies have shown that R domain deletions and missense mutations in this region of the R domain generate band C (mature) protein (see Vankeerberghen et al., 1999, *Biochemistry* 38:14988-14998; and Vankeerberghen et al., 1998, *Hum. Mol. Genet.* 7:1761-1769). Other studies have also shown that elimination of a single arginine-framed motif (residues 764-766) did not impair processing (Chang et al., 1999, *Mol. Cell* 4:137-142).

The CFTR proteins comprising partially deleted R domains of the present invention reveal several aspects of R domain function. a) Length. In general, the more the R domain deleted, the less the Cl^- current. However, length alone does explain the results as evidenced by the finding that Δ708-783/823-835 (267 bp deleted) had as much current as Δ708-723/749-783/819-835 (204 bp deleted). b) Specific phosphoserines. Although all of the CFTR proteins of the present invention retained Ser660 and Ser700, the number of additional phosphoserines failed to predict the amount of current. For example, Δ760-835 (with one additional phosphoserine) had at least as much current as Δ708-783 (two additional phosphoserines) and Δ708-723/749-783/819-835 (three additional phosphoserines). These results are consistent with previous work suggesting that not all the phosphoserines are necessary for activity and no one phosphoserine is dominant. c) Charge. No correlation between Cl^- current and net charge present within the region between aa 708 and 835 was found. d) Ser737. Mutation of Ser737 suggested it has an inhibitory function on CFTR studied in Xenopus oocytes (Wilkinson et al., 1997, *Am J. Physiol.* 273:L127-L133). In airway epithelia, the CFTR proteins comprising partially deleted R domains of the present invention did not reveal inhibition. e) Residues 817-838. This stretch of negatively charged amino acids has been suggested as a stimulatory region (Xie et al., 2000, *Biophys. J.* 78:1293-1305). Deletion of this region decreased current in Δ708-723/749-783/819-835 compared to Δ708-723/749-783/832-835. However, deletion of this region in Δ708-783/823-835 did not reduce current as compared to Δ708-783. f) Residues 760-783. It was previously suggested that these residues prevented constitutive activity (Baldursson et al., 2001, *J. Biol. Chem.* 276:1904-1910). The present invention provides support for this hypothesis. g) Structure. The ability to alter the sequence of the R domain in so many different ways and yet retain Cl^- channel function and phosphorylation-dependent activity supports the hypothesis that there are few or no required structural motifs in this portion of the R domain. That conclusion is consistent with the recent finding that this region of the R domain is predominantly random coil (Ostedgaard et al., 2000, *Proc. Natl. Acad. Sci.* 97:5657-5662).

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     15                  20                  25

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Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                 100                 105

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Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

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Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
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Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

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        160                 165                 170

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    175                 180                 185

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Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

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Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

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Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

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Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

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tgg aac aca tac ctt cga tat att act gtc cac aag agc tta att ttt     2331
Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe
        720                 725                 730

gtg cta att tgg tgc tta gta att ttt ctg gca gag gtg gct gct tct     2379
Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser
    735                 740                 745

ttg gtt gtg ctg tgg ctc ctt gga aac act cct ctt caa gac aaa ggg     2427
Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly
750                 755                 760                 765

aat agt act cat agt aga aat aac agc tat gca gtg att atc acc agc     2475
Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser
                770                 775                 780

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            785                 790                 795

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Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu
    815                 820                 825

caa gca cct atg tca acc ctc aac acg ttg aaa gca ggt ggg att ctt     2667
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830                 835                 840                 845

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Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu
                850                 855                 860

acc ata ttt gac ttc atc cag ttg tta tta att gtg att gga gct ata     2763
Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile
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gca gtt gtc gca gtt tta caa ccc tac atc ttt gtt gca aca gtg cca     2811
Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro
        880                 885                 890

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Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser
    895                 900                 905

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Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr
910                 915                 920                 925

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His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly
                930                 935                 940

cgg cag cct tac ttt gaa act ctg ttc cac aaa gct ctg aat tta cat     3003
Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His
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Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met
        960                 965                 970

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Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys
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Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp
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gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                  10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
             65                  70                  75

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Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
         80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                 100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
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           225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
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Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
                690                 695                 700

ctc aat cca atc aac tct acg ctt cag gca cga agg agg cag tct gtc     2283
Leu Asn Pro Ile Asn Ser Thr Leu Gln Ala Arg Arg Arg Gln Ser Val
            705                 710                 715

ctg aac ctg atg aca cac tca gtt aac caa ggt cag aac att cac cga     2331
Leu Asn Leu Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His Arg
        720                 725                 730

aag aca aca gca tcc aca cga aaa gtg tca ctg gcc cct cag gca aac     2379
Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn
    735                 740                 745

ttg act gaa ctg gat ata tat tca aga agg tta tct caa gaa act ggc     2427
Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly
750                 755                 760                 765

ttg gaa ata agt gaa gaa att aac gaa gaa gac tta aag gag tgc ttt     2475
Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Cys Phe
                770                 775                 780

ttt gat gat atg gag agc ata cca gca gtg act aca tgg aac aca tac     2523
Phe Asp Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr
            785                 790                 795

ctt cga tat att act gtc cac aag agc tta att ttt gtg cta att tgg     2571
Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp
        800                 805                 810

tgc tta gta att ttt ctg gca gag gtg gct gct tct ttg gtt gtg ctg     2619
Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu
    815                 820                 825

tgg ctc ctt gga aac act cct ctt caa gac aaa ggg aat agt act cat     2667
Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His
830                 835                 840                 845

agt aga aat aac agc tat gca gtg att atc acc agc acc agt tcg tat     2715
Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr
                850                 855                 860
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tat gtg ttt tac att tac gtg gga gta gcc gac act ttg ctt gct atg     2763
Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met
            865                 870                 875

gga ttc ttc aga ggt cta cca ctg gtg cat act cta atc aca gtg tcg     2811
Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser
        880                 885                 890

aaa att tta cac cac aaa atg tta cat tct gtt ctt caa gca cct atg     2859
Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met
    895                 900                 905

tca acc ctc aac acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc     2907
Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser
910                 915                 920                 925

aaa gat ata gca att ttg gat gac ctt ctg cct ctt acc ata ttt gac     2955
Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp
                930                 935                 940

ttc atc cag ttg tta tta att gtg att gga gct ata gca gtt gtc gca     3003
Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala
            945                 950                 955

gtt tta caa ccc tac atc ttt gtt gca aca gtg cca gtg ata gtg gct     3051
Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala
        960                 965                 970

ttt att atg ttg aga gca tat ttc ctc caa acc tca cag caa ctc aaa     3099
Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys
    975                 980                 985

caa ctg gaa tct gaa ggc agg agt cca att ttc act cat ctt gtt aca     3147
Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr
 990                 995                1000                1005

agc tta aaa gga cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac     3195
Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr
                1010                1015                1020

ttt gaa act ctg ttc cac aaa gct ctg aat tta cat act gcc aac tgg     3243
Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp
            1025                1030                1035

ttc ttg tac ctg tca aca ctg cgc tgg ttc caa atg aga ata gaa atg     3291
Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met
        1040                1045                1050

att ttt gtc atc ttc ttc att gct gtt acc ttc att tcc att tta aca     3339
Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr
    1055                1060                1065

aca gga gaa gga gaa gga aga gtt ggt att atc ctg act tta gcc atg     3387
Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met
1070                1075                1080                1085

aat atc atg agt aca ttg cag tgg gct gta aac tcc agc ata gat gtg     3435
Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val
                1090                1095                1100

gat agc ttg atg cga tct gtg agc cga gtc ttt aag ttc att gac atg     3483
Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met
            1105                1110                1115

cca aca gaa ggt aaa cct acc aag tca acc aaa cca tac aag aat ggc     3531
Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly
        1120                1125                1130

caa ctc tcg aaa gtt atg att att gag aat tca cac gtg aag aaa gat     3579
Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp
    1135                1140                1145

gac atc tgg ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca     3627
Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala
1150                1155                1160                1165

aaa tac aca gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca     3675
Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser
                1170                1175                1180
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ata agt cct ggc cag agg gtg ggc ctc ttg gga aga act gga tca ggg     3723
Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly
            1185                1190                1195

aag agt act ttg tta tca gct ttt ttg aga cta ctg aac act gaa gga     3771
Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly
        1200                1205                1210

gaa atc cag atc gat ggt gtg tct tgg gat tca ata act ttg caa cag     3819
Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln
    1215                1220                1225

tgg agg aaa gcc ttt gga gtg ata cca cag aaa gta ttt att ttt tct     3867
Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser
1230                1235                1240                1245

gga aca ttt aga aaa aac ttg gat ccc tat gaa cag tgg agt gat caa     3915
Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln
                1250                1255                1260

gaa ata tgg aaa gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa     3963
Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu
            1265                1270                1275

cag ttt cct ggg aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc     4011
Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val
        1280                1285                1290

cta agc cat ggc cac aag cag ttg atg tgc ttg gct aga tct gtt ctc     4059
Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu
    1295                1300                1305

agt aag gcg aag atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat     4107
Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp
1310                1315                1320                1325

cca gta aca tac caa ata att aga aga act cta aaa caa gca ttt gct     4155
Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala
                1330                1335                1340

gat tgc aca gta att ctc tgt gaa cac agg ata gaa gca atg ctg gaa     4203
Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu
            1345                1350                1355

tgc caa caa ttt ttg gtc ata gaa gag aac aaa gtg cgg cag tac gat     4251
Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp
        1360                1365                1370

tcc atc cag aaa ctg ctg aac gag agg agc ctc ttc cgg caa gcc atc     4299
Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile
    1375                1380                1385

agc ccc tcc gac agg gtg aag ctc ttt ccc cac cgg aac tca agc aag     4347
Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys
1390                1395                1400                1405

tgc aag tct aag ccc cag att gct gct ctg aaa gag gag aca gaa gaa     4395
Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu
                1410                1415                1420

gag gtg caa gat aca agg ctt tag                                    4419
Glu Val Gln Asp Thr Arg Leu  *
            1425
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<210> SEQ ID NO 3
<211> LENGTH: 4410
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gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccagc    120
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gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                  10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
             65                  70                  75

ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc      411
Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
         80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                  100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
            225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
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            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
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Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
                690                 695                 700

ctc aat cca atc aac tct atc gaa gag gat tct gat gag cct tta gag     2283
Leu Asn Pro Ile Asn Ser Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu
            705                 710                 715

aga agg ctg tcc tta gta cca gat tct gag cag gga gag gcg ata cac     2331
Arg Arg Leu Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile His
        720                 725                 730

cga aag aca aca gca tcc aca cga aaa gtg tca ctg gcc cct cag gca     2379
Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala
    735                 740                 745

aac ttg act gaa ctg gat ata tat tca aga agg tta tct caa gaa act     2427
Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr
750                 755                 760                 765

ggc ttg gaa ata agt gaa gaa att aac gaa gaa gac tta aag gag gat     2475
Gly Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Asp
                770                 775                 780

atg gag agc ata cca gca gtg act aca tgg aac aca tac ctt cga tat     2523
Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr
            785                 790                 795

att act gtc cac aag agc tta att ttt gtg cta att tgg tgc tta gta     2571
Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val
        800                 805                 810

att ttt ctg gca gag gtg gct gct tct ttg gtt gtg ctg tgg ctc ctt     2619
Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu
    815                 820                 825

gga aac act cct ctt caa gac aaa ggg aat agt act cat agt aga aat     2667
Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn
830                 835                 840                 845

aac agc tat gca gtg att atc acc agc acc agt tcg tat tat gtg ttt     2715
Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe
                850                 855                 860

tac att tac gtg gga gta gcc gac act ttg ctt gct atg gga ttc ttc     2763
Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe
            865                 870                 875

aga ggt cta cca ctg gtg cat act cta atc aca gtg tcg aaa att tta     2811
Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu
        880                 885                 890

cac cac aaa atg tta cat tct gtt ctt caa gca cct atg tca acc ctc     2859
His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu
    895                 900                 905

aac acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc aaa gat ata     2907
Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile
910                 915                 920                 925

gca att ttg gat gac ctt ctg cct ctt acc ata ttt gac ttc atc cag     2955
Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln
                930                 935                 940
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ttg tta tta att gtg att gga gct ata gca gtt gtc gca gtt tta caa     3003
Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln
            945                 950                 955

ccc tac atc ttt gtt gca aca gtg cca gtg ata gtg gct ttt att atg     3051
Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met
        960                 965                 970

ttg aga gca tat ttc ctc caa acc tca cag caa ctc aaa caa ctg gaa     3099
Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu
    975                 980                 985

tct gaa ggc agg agt cca att ttc act cat ctt gtt aca agc tta aaa     3147
Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys
 990                 995                1000                1005

gga cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac ttt gaa act     3195
Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr
                1010                1015                1020

ctg ttc cac aaa gct ctg aat tta cat act gcc aac tgg ttc ttg tac     3243
Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr
            1025                1030                1035

ctg tca aca ctg cgc tgg ttc caa atg aga ata gaa atg att ttt gtc     3291
Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val
        1040                1045                1050

atc ttc ttc att gct gtt acc ttc att tcc att tta aca aca gga gaa     3339
Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu
    1055                1060                1065

gga gaa gga aga gtt ggt att atc ctg act tta gcc atg aat atc atg     3387
Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met
1070                1075                1080                1085

agt aca ttg cag tgg gct gta aac tcc agc ata gat gtg gat agc ttg     3435
Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu
                1090                1095                1100

atg cga tct gtg agc cga gtc ttt aag ttc att gac atg cca aca gaa     3483
Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu
            1105                1110                1115

ggt aaa cct acc aag tca acc aaa cca tac aag aat ggc caa ctc tcg     3531
Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser
        1120                1125                1130

aaa gtt atg att att gag aat tca cac gtg aag aaa gat gac atc tgg     3579
Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp
    1135                1140                1145

ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca aaa tac aca     3627
Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr
1150                1155                1160                1165

gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca ata agt cct     3675
Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro
                1170                1175                1180

ggc cag agg gtg ggc ctc ttg gga aga act gga tca ggg aag agt act     3723
Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr
            1185                1190                1195

ttg tta tca gct ttt ttg aga cta ctg aac act gaa gga gaa atc cag     3771
Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln
        1200                1205                1210

atc gat ggt gtg tct tgg gat tca ata act ttg caa cag tgg agg aaa     3819
Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys
    1215                1220                1225

gcc ttt gga gtg ata cca cag aaa gta ttt att ttt tct gga aca ttt     3867
Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe
1230                1235                1240                1245

aga aaa aac ttg gat ccc tat gaa cag tgg agt gat caa gaa ata tgg     3915
Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp
                1250                1255                1260
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aaa gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa cag ttt cct     3963
Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro
            1265                1270                1275

ggg aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc cta agc cat     4011
Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His
        1280                1285                1290

ggc cac aag cag ttg atg tgc ttg gct aga tct gtt ctc agt aag gcg     4059
Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala
    1295                1300                1305

aag atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat cca gta aca     4107
Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr
1310                1315                1320                1325

tac caa ata att aga aga act cta aaa caa gca ttt gct gat tgc aca     4155
Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr
                1330                1335                1340

gta att ctc tgt gaa cac agg ata gaa gca atg ctg gaa tgc caa caa     4203
Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln
            1345                1350                1355

ttt ttg gtc ata gaa gag aac aaa gtg cgg cag tac gat tcc atc cag     4251
Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln
        1360                1365                1370

aaa ctg ctg aac gag agg agc ctc ttc cgg caa gcc atc agc ccc tcc     4299
Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser
    1375                1380                1385

gac agg gtg aag ctc ttt ccc cac cgg aac tca agc aag tgc aag tct     4347
Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser
1390                1395                1400                1405

aag ccc cag att gct gct ctg aaa gag gag aca gaa gaa gag gtg caa     4395
Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln
                1410                1415                1420

gat aca agg ctt tag                                                4410
Asp Thr Arg Leu  *
            1425


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gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                  10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
             65                  70                  75
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ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc      411
Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
         80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                 100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
            225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
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            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
                690                 695                 700

ctc aat cca atc aac tct atc gaa gag gat tct gat gag cct tta gag     2283
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Leu Asn Pro Ile Asn Ser Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu
            705                 710                 715

aga agg ctg tcc tta gta cca gat tct gag cag gga gag gcg ata cac     2331
Arg Arg Leu Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile His
        720                 725                 730

cga aag aca aca gca tcc aca cga aaa gtg tca ctg gcc cct cag gca     2379
Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala
    735                 740                 745

aac ttg act gaa ctg gat ata tat tca aga agg tta tct caa gaa act     2427
Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr
750                 755                 760                 765

ggc ttg gat atg gag agc ata cca gca gtg act aca tgg aac aca tac     2475
Gly Leu Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr
                770                 775                 780

ctt cga tat att act gtc cac aag agc tta att ttt gtg cta att tgg     2523
Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp
            785                 790                 795

tgc tta gta att ttt ctg gca gag gtg gct gct tct ttg gtt gtg ctg     2571
Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu
        800                 805                 810

tgg ctc ctt gga aac act cct ctt caa gac aaa ggg aat agt act cat     2619
Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His
    815                 820                 825

agt aga aat aac agc tat gca gtg att atc acc agc acc agt tcg tat     2667
Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr
830                 835                 840                 845

tat gtg ttt tac att tac gtg gga gta gcc gac act ttg ctt gct atg     2715
Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met
                850                 855                 860

gga ttc ttc aga ggt cta cca ctg gtg cat act cta atc aca gtg tcg     2763
Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser
            865                 870                 875

aaa att tta cac cac aaa atg tta cat tct gtt ctt caa gca cct atg     2811
Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met
        880                 885                 890

tca acc ctc aac acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc     2859
Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser
    895                 900                 905

aaa gat ata gca att ttg gat gac ctt ctg cct ctt acc ata ttt gac     2907
Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp
910                 915                 920                 925

ttc atc cag ttg tta tta att gtg att gga gct ata gca gtt gtc gca     2955
Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala
                930                 935                 940

gtt tta caa ccc tac atc ttt gtt gca aca gtg cca gtg ata gtg gct     3003
Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala
            945                 950                 955

ttt att atg ttg aga gca tat ttc ctc caa acc tca cag caa ctc aaa     3051
Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys
        960                 965                 970

caa ctg gaa tct gaa ggc agg agt cca att ttc act cat ctt gtt aca     3099
Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr
    975                 980                 985

agc tta aaa gga cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac     3147
Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr
 990                 995                1000                1005

ttt gaa act ctg ttc cac aaa gct ctg aat tta cat act gcc aac tgg     3195
Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp
                1010                1015                1020
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ttc ttg tac ctg tca aca ctg cgc tgg ttc caa atg aga ata gaa atg     3243
Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met
            1025                1030                1035

att ttt gtc atc ttc ttc att gct gtt acc ttc att tcc att tta aca     3291
Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr
        1040                1045                1050

aca gga gaa gga gaa gga aga gtt ggt att atc ctg act tta gcc atg     3339
Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met
    1055                1060                1065

aat atc atg agt aca ttg cag tgg gct gta aac tcc agc ata gat gtg     3387
Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val
1070                1075                1080                1085

gat agc ttg atg cga tct gtg agc cga gtc ttt aag ttc att gac atg     3435
Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met
                1090                1095                1100

cca aca gaa ggt aaa cct acc aag tca acc aaa cca tac aag aat ggc     3483
Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly
            1105                1110                1115

caa ctc tcg aaa gtt atg att att gag aat tca cac gtg aag aaa gat     3531
Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp
        1120                1125                1130

gac atc tgg ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca     3579
Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala
    1135                1140                1145

aaa tac aca gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca     3627
Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser
1150                1155                1160                1165

ata agt cct ggc cag agg gtg ggc ctc ttg gga aga act gga tca ggg     3675
Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly
                1170                1175                1180

aag agt act ttg tta tca gct ttt ttg aga cta ctg aac act gaa gga     3723
Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly
            1185                1190                1195

gaa atc cag atc gat ggt gtg tct tgg gat tca ata act ttg caa cag     3771
Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln
        1200                1205                1210

tgg agg aaa gcc ttt gga gtg ata cca cag aaa gta ttt att ttt tct     3819
Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser
    1215                1220                1225

gga aca ttt aga aaa aac ttg gat ccc tat gaa cag tgg agt gat caa     3867
Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln
1230                1235                1240                1245

gaa ata tgg aaa gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa     3915
Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu
                1250                1255                1260

cag ttt cct ggg aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc     3963
Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val
            1265                1270                1275

cta agc cat ggc cac aag cag ttg atg tgc ttg gct aga tct gtt ctc     4011
Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu
        1280                1285                1290

agt aag gcg aag atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat     4059
Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp
    1295                1300                1305

cca gta aca tac caa ata att aga aga act cta aaa caa gca ttt gct     4107
Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala
1310                1315                1320                1325

gat tgc aca gta att ctc tgt gaa cac agg ata gaa gca atg ctg gaa     4155
Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu
                1330                1335                1340
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tgc caa caa ttt ttg gtc ata gaa gag aac aaa gtg cgg cag tac gat     4203
Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp
            1345                1350                1355

tcc atc cag aaa ctg ctg aac gag agg agc ctc ttc cgg caa gcc atc     4251
Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile
        1360                1365                1370

agc ccc tcc gac agg gtg aag ctc ttt ccc cac cgg aac tca agc aag     4299
Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys
    1375                1380                1385

tgc aag tct aag ccc cag att gct gct ctg aaa gag gag aca gaa gaa     4347
Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu
1390                1395                1400                1405

gag gtg caa gat aca agg ctt tag                                    4371
Glu Val Gln Asp Thr Arg Leu  *
                1410


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gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                   10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
             65                  70                  75

ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc      411
Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
         80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                  100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170
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aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
            225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
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        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
                690                 695                 700

ctc aat cca atc aac tct acg ctt cag gca cga agg agg cag tct gtc     2283
Leu Asn Pro Ile Asn Ser Thr Leu Gln Ala Arg Arg Arg Gln Ser Val
            705                 710                 715

ctg aac ctg atg aca cac tca gtt aac caa ggt cag aac att cac cga     2331
Leu Asn Leu Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His Arg
        720                 725                 730

aag aca aca gca tcc aca cga aaa gtg tca ctg gcc cct cag gca aac     2379
Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn
    735                 740                 745

ttg act gaa ctg gat ata tat tca aga agg tta tct caa gaa act ggc     2427
Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly
750                 755                 760                 765

ttg gat atg gag agc ata cca gca gtg act aca tgg aac aca tac ctt     2475
Leu Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu
                770                 775                 780

cga tat att act gtc cac aag agc tta att ttt gtg cta att tgg tgc     2523
Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys
            785                 790                 795

tta gta att ttt ctg gca gag gtg gct gct tct ttg gtt gtg ctg tgg     2571
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Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp
        800                 805                 810

ctc ctt gga aac act cct ctt caa gac aaa ggg aat agt act cat agt     2619
Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser
    815                 820                 825

aga aat aac agc tat gca gtg att atc acc agc acc agt tcg tat tat     2667
Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr
830                 835                 840                 845

gtg ttt tac att tac gtg gga gta gcc gac act ttg ctt gct atg gga     2715
Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly
                850                 855                 860

ttc ttc aga ggt cta cca ctg gtg cat act cta atc aca gtg tcg aaa     2763
Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys
            865                 870                 875

att tta cac cac aaa atg tta cat tct gtt ctt caa gca cct atg tca     2811
Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser
        880                 885                 890

acc ctc aac acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc aaa     2859
Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys
    895                 900                 905

gat ata gca att ttg gat gac ctt ctg cct ctt acc ata ttt gac ttc     2907
Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe
910                 915                 920                 925

atc cag ttg tta tta att gtg att gga gct ata gca gtt gtc gca gtt     2955
Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val
                930                 935                 940

tta caa ccc tac atc ttt gtt gca aca gtg cca gtg ata gtg gct ttt     3003
Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe
            945                 950                 955

att atg ttg aga gca tat ttc ctc caa acc tca cag caa ctc aaa caa     3051
Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln
        960                 965                 970

ctg gaa tct gaa ggc agg agt cca att ttc act cat ctt gtt aca agc     3099
Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser
    975                 980                 985

tta aaa gga cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac ttt     3147
Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe
 990                 995                1000                1005

gaa act ctg ttc cac aaa gct ctg aat tta cat act gcc aac tgg ttc     3195
Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe
                1010                1015                1020

ttg tac ctg tca aca ctg cgc tgg ttc caa atg aga ata gaa atg att     3243
Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile
            1025                1030                1035

ttt gtc atc ttc ttc att gct gtt acc ttc att tcc att tta aca aca     3291
Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr
        1040                1045                1050

gga gaa gga gaa gga aga gtt ggt att atc ctg act tta gcc atg aat     3339
Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn
    1055                1060                1065

atc atg agt aca ttg cag tgg gct gta aac tcc agc ata gat gtg gat     3387
Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp
1070                1075                1080                1085

agc ttg atg cga tct gtg agc cga gtc ttt aag ttc att gac atg cca     3435
Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro
                1090                1095                1100

aca gaa ggt aaa cct acc aag tca acc aaa cca tac aag aat ggc caa     3483
Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln
            1105                1110                1115
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ctc tcg aaa gtt atg att att gag aat tca cac gtg aag aaa gat gac     3531
Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp
        1120                1125                1130

atc tgg ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca aaa     3579
Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys
    1135                1140                1145

tac aca gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca ata     3627
Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile
1150                1155                1160                1165

agt cct ggc cag agg gtg ggc ctc ttg gga aga act gga tca ggg aag     3675
Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys
                1170                1175                1180

agt act ttg tta tca gct ttt ttg aga cta ctg aac act gaa gga gaa     3723
Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu
            1185                1190                1195

atc cag atc gat ggt gtg tct tgg gat tca ata act ttg caa cag tgg     3771
Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp
        1200                1205                1210

agg aaa gcc ttt gga gtg ata cca cag aaa gta ttt att ttt tct gga     3819
Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly
    1215                1220                1225

aca ttt aga aaa aac ttg gat ccc tat gaa cag tgg agt gat caa gaa     3867
Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu
1230                1235                1240                1245

ata tgg aaa gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa cag     3915
Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln
                1250                1255                1260

ttt cct ggg aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc cta     3963
Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu
            1265                1270                1275

agc cat ggc cac aag cag ttg atg tgc ttg gct aga tct gtt ctc agt     4011
Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser
        1280                1285                1290

aag gcg aag atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat cca     4059
Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro
    1295                1300                1305

gta aca tac caa ata att aga aga act cta aaa caa gca ttt gct gat     4107
Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp
1310                1315                1320                1325

tgc aca gta att ctc tgt gaa cac agg ata gaa gca atg ctg gaa tgc     4155
Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys
                1330                1335                1340

caa caa ttt ttg gtc ata gaa gag aac aaa gtg cgg cag tac gat tcc     4203
Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser
            1345                1350                1355

atc cag aaa ctg ctg aac gag agg agc ctc ttc cgg caa gcc atc agc     4251
Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser
        1360                1365                1370

ccc tcc gac agg gtg aag ctc ttt ccc cac cgg aac tca agc aag tgc     4299
Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys
    1375                1380                1385

aag tct aag ccc cag att gct gct ctg aaa gag gag aca gaa gaa gag     4347
Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu
1390                1395                1400                1405

gtg caa gat aca agg ctt tag                                        4368
Val Gln Asp Thr Arg Leu  *
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aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca     60

gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccagc    120

gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                  10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
             65                  70                  75

ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc      411
Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
         80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                 100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
            225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265
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caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
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    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
                690                 695                 700

ctc aat cca atc aac tct ata cga aaa ttt tcc att gtg caa aag act     2283
Leu Asn Pro Ile Asn Ser Ile Arg Lys Phe Ser Ile Val Gln Lys Thr
            705                 710                 715

ccc tta caa atg aat ggc atc gaa gag gat tct gat gag cct tta gag     2331
Pro Leu Gln Met Asn Gly Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu
        720                 725                 730

aga agg ctg tcc tta gta cca gat tct gag cag gga gag gcg ata ctg     2379
Arg Arg Leu Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile Leu
    735                 740                 745

cct cgc atc agc gtg atc agc act ggc ccc gat atg gag agc ata cca     2427
Pro Arg Ile Ser Val Ile Ser Thr Gly Pro Asp Met Glu Ser Ile Pro
750                 755                 760                 765

gca gtg act aca tgg aac aca tac ctt cga tat att act gtc cac aag     2475
Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys
                770                 775                 780

agc tta att ttt gtg cta att tgg tgc tta gta att ttt ctg gca gag     2523
Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu
            785                 790                 795

gtg gct gct tct ttg gtt gtg ctg tgg ctc ctt gga aac act cct ctt     2571
Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu
        800                 805                 810

caa gac aaa ggg aat agt act cat agt aga aat aac agc tat gca gtg     2619
Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val
    815                 820                 825

att atc acc agc acc agt tcg tat tat gtg ttt tac att tac gtg gga     2667
Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val Gly
830                 835                 840                 845

gta gcc gac act ttg ctt gct atg gga ttc ttc aga ggt cta cca ctg     2715
Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro Leu
                850                 855                 860

gtg cat act cta atc aca gtg tcg aaa att tta cac cac aaa atg tta     2763
Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu
            865                 870                 875

cat tct gtt ctt caa gca cct atg tca acc ctc aac acg ttg aaa gca     2811
His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn Thr Leu Lys Ala
        880                 885                 890

ggt ggg att ctt aat aga ttc tcc aaa gat ata gca att ttg gat gac     2859
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Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp Asp
    895                 900                 905

ctt ctg cct ctt acc ata ttt gac ttc atc cag ttg tta tta att gtg     2907
Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu Ile Val
910                 915                 920                 925

att gga gct ata gca gtt gtc gca gtt tta caa ccc tac atc ttt gtt     2955
Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe Val
                930                 935                 940

gca aca gtg cca gtg ata gtg gct ttt att atg ttg aga gca tat ttc     3003
Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr Phe
            945                 950                 955

ctc caa acc tca cag caa ctc aaa caa ctg gaa tct gaa ggc agg agt     3051
Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser
        960                 965                 970

cca att ttc act cat ctt gtt aca agc tta aaa gga cta tgg aca ctt     3099
Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu
    975                 980                 985

cgt gcc ttc gga cgg cag cct tac ttt gaa act ctg ttc cac aaa gct     3147
Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala
 990                 995                1000                1005

ctg aat tta cat act gcc aac tgg ttc ttg tac ctg tca aca ctg cgc     3195
Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg
                1010                1015                1020

tgg ttc caa atg aga ata gaa atg att ttt gtc atc ttc ttc att gct     3243
Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile Ala
            1025                1030                1035

gtt acc ttc att tcc att tta aca aca gga gaa gga gaa gga aga gtt     3291
Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg Val
        1040                1045                1050

ggt att atc ctg act tta gcc atg aat atc atg agt aca ttg cag tgg     3339
Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu Gln Trp
    1055                1060                1065

gct gta aac tcc agc ata gat gtg gat agc ttg atg cga tct gtg agc     3387
Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met Arg Ser Val Ser
1070                1075                1080                1085

cga gtc ttt aag ttc att gac atg cca aca gaa ggt aaa cct acc aag     3435
Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly Lys Pro Thr Lys
                1090                1095                1100

tca acc aaa cca tac aag aat ggc caa ctc tcg aaa gtt atg att att     3483
Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser Lys Val Met Ile Ile
            1105                1110                1115

gag aat tca cac gtg aag aaa gat gac atc tgg ccc tca ggg ggc caa     3531
Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly Gln
        1120                1125                1130

atg act gtc aaa gat ctc aca gca aaa tac aca gaa ggt gga aat gcc     3579
Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly Asn Ala
    1135                1140                1145

ata tta gag aac att tcc ttc tca ata agt cct ggc cag agg gtg ggc     3627
Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg Val Gly
1150                1155                1160                1165

ctc ttg gga aga act gga tca ggg aag agt act ttg tta tca gct ttt     3675
Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser Ala Phe
                1170                1175                1180

ttg aga cta ctg aac act gaa gga gaa atc cag atc gat ggt gtg tct     3723
Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly Val Ser
            1185                1190                1195

tgg gat tca ata act ttg caa cag tgg agg aaa gcc ttt gga gtg ata     3771
Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly Val Ile
        1200                1205                1210
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cca cag aaa gta ttt att ttt tct gga aca ttt aga aaa aac ttg gat     3819
Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn Leu Asp
    1215                1220                1225

ccc tat gaa cag tgg agt gat caa gaa ata tgg aaa gtt gca gat gag     3867
Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp Lys Val Ala Asp Glu
1230                1235                1240                1245

gtt ggg ctc aga tct gtg ata gaa cag ttt cct ggg aag ctt gac ttt     3915
Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe
                1250                1255                1260

gtc ctt gtg gat ggg ggc tgt gtc cta agc cat ggc cac aag cag ttg     3963
Val Leu Val Asp Gly Gly Cys Val Leu Ser His Gly His Lys Gln Leu
            1265                1270                1275

atg tgc ttg gct aga tct gtt ctc agt aag gcg aag atc ttg ctg ctt     4011
Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu Leu
        1280                1285                1290

gat gaa ccc agt gct cat ttg gat cca gta aca tac caa ata att aga     4059
Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile Ile Arg
    1295                1300                1305

aga act cta aaa caa gca ttt gct gat tgc aca gta att ctc tgt gaa     4107
Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val Ile Leu Cys Glu
1310                1315                1320                1325

cac agg ata gaa gca atg ctg gaa tgc caa caa ttt ttg gtc ata gaa     4155
His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe Leu Val Ile Glu
                1330                1335                1340

gag aac aaa gtg cgg cag tac gat tcc atc cag aaa ctg ctg aac gag     4203
Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu Asn Glu
            1345                1350                1355

agg agc ctc ttc cgg caa gcc atc agc ccc tcc gac agg gtg aag ctc     4251
Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser Asp Arg Val Lys Leu
        1360                1365                1370

ttt ccc cac cgg aac tca agc aag tgc aag tct aag ccc cag att gct     4299
Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln Ile Ala
    1375                1380                1385

gct ctg aaa gag gag aca gaa gaa gag gtg caa gat aca agg ctt tag     4347
Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln Asp Thr Arg Leu  *
1390                1395                1400


<210> SEQ ID NO 7
<211> LENGTH: 4347
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gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                  10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60
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gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
            65                  70                  75

ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc      411
Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
        80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
    95                  100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
            225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380
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aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
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                690                 695                 700

ctc aat cca atc aac tct cac cga aag aca aca gca tcc aca cga aaa     2283
Leu Asn Pro Ile Asn Ser His Arg Lys Thr Thr Ala Ser Thr Arg Lys
            705                 710                 715

gtg tca ctg gcc cct cag gca aac ttg act gaa ctg gat ata tat tca     2331
Val Ser Leu Ala Pro Gln Ala Asn Leu Thr Glu Leu Asp Ile Tyr Ser
        720                 725                 730

aga agg tta tct caa gaa act ggc ttg gaa ata agt gaa gaa att aac     2379
Arg Arg Leu Ser Gln Glu Thr Gly Leu Glu Ile Ser Glu Glu Ile Asn
    735                 740                 745

gaa gaa gac tta aag gag tgc ttt ttt gat gat atg gag agc ata cca     2427
Glu Glu Asp Leu Lys Glu Cys Phe Phe Asp Asp Met Glu Ser Ile Pro
750                 755                 760                 765

gca gtg act aca tgg aac aca tac ctt cga tat att act gtc cac aag     2475
Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys
                770                 775                 780

agc tta att ttt gtg cta att tgg tgc tta gta att ttt ctg gca gag     2523
Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu
            785                 790                 795

gtg gct gct tct ttg gtt gtg ctg tgg ctc ctt gga aac act cct ctt     2571
Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu
        800                 805                 810

caa gac aaa ggg aat agt act cat agt aga aat aac agc tat gca gtg     2619
Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val
    815                 820                 825

att atc acc agc acc agt tcg tat tat gtg ttt tac att tac gtg gga     2667
Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val Gly
830                 835                 840                 845

gta gcc gac act ttg ctt gct atg gga ttc ttc aga ggt cta cca ctg     2715
Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro Leu
                850                 855                 860

gtg cat act cta atc aca gtg tcg aaa att tta cac cac aaa atg tta     2763
Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu
            865                 870                 875

cat tct gtt ctt caa gca cct atg tca acc ctc aac acg ttg aaa gca     2811
His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn Thr Leu Lys Ala
        880                 885                 890

ggt ggg att ctt aat aga ttc tcc aaa gat ata gca att ttg gat gac     2859
Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp Asp
    895                 900                 905

ctt ctg cct ctt acc ata ttt gac ttc atc cag ttg tta tta att gtg     2907
Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu Ile Val
910                 915                 920                 925

att gga gct ata gca gtt gtc gca gtt tta caa ccc tac atc ttt gtt     2955
Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe Val
                930                 935                 940

gca aca gtg cca gtg ata gtg gct ttt att atg ttg aga gca tat ttc     3003
Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr Phe
            945                 950                 955

ctc caa acc tca cag caa ctc aaa caa ctg gaa tct gaa ggc agg agt     3051
Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser
        960                 965                 970

cca att ttc act cat ctt gtt aca agc tta aaa gga cta tgg aca ctt     3099
Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu
    975                 980                 985

cgt gcc ttc gga cgg cag cct tac ttt gaa act ctg ttc cac aaa gct     3147
Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala
 990                 995                1000                1005

ctg aat tta cat act gcc aac tgg ttc ttg tac ctg tca aca ctg cgc     3195
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Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg
                1010                1015                1020

tgg ttc caa atg aga ata gaa atg att ttt gtc atc ttc ttc att gct     3243
Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile Ala
            1025                1030                1035

gtt acc ttc att tcc att tta aca aca gga gaa gga gaa gga aga gtt     3291
Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg Val
        1040                1045                1050

ggt att atc ctg act tta gcc atg aat atc atg agt aca ttg cag tgg     3339
Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu Gln Trp
    1055                1060                1065

gct gta aac tcc agc ata gat gtg gat agc ttg atg cga tct gtg agc     3387
Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met Arg Ser Val Ser
1070                1075                1080                1085

cga gtc ttt aag ttc att gac atg cca aca gaa ggt aaa cct acc aag     3435
Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly Lys Pro Thr Lys
                1090                1095                1100

tca acc aaa cca tac aag aat ggc caa ctc tcg aaa gtt atg att att     3483
Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser Lys Val Met Ile Ile
            1105                1110                1115

gag aat tca cac gtg aag aaa gat gac atc tgg ccc tca ggg ggc caa     3531
Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly Gln
        1120                1125                1130

atg act gtc aaa gat ctc aca gca aaa tac aca gaa ggt gga aat gcc     3579
Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly Asn Ala
    1135                1140                1145

ata tta gag aac att tcc ttc tca ata agt cct ggc cag agg gtg ggc     3627
Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg Val Gly
1150                1155                1160                1165

ctc ttg gga aga act gga tca ggg aag agt act ttg tta tca gct ttt     3675
Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser Ala Phe
                1170                1175                1180

ttg aga cta ctg aac act gaa gga gaa atc cag atc gat ggt gtg tct     3723
Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly Val Ser
            1185                1190                1195

tgg gat tca ata act ttg caa cag tgg agg aaa gcc ttt gga gtg ata     3771
Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly Val Ile
        1200                1205                1210

cca cag aaa gta ttt att ttt tct gga aca ttt aga aaa aac ttg gat     3819
Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn Leu Asp
    1215                1220                1225

ccc tat gaa cag tgg agt gat caa gaa ata tgg aaa gtt gca gat gag     3867
Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp Lys Val Ala Asp Glu
1230                1235                1240                1245

gtt ggg ctc aga tct gtg ata gaa cag ttt cct ggg aag ctt gac ttt     3915
Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe
                1250                1255                1260

gtc ctt gtg gat ggg ggc tgt gtc cta agc cat ggc cac aag cag ttg     3963
Val Leu Val Asp Gly Gly Cys Val Leu Ser His Gly His Lys Gln Leu
            1265                1270                1275

atg tgc ttg gct aga tct gtt ctc agt aag gcg aag atc ttg ctg ctt     4011
Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu Leu
        1280                1285                1290

gat gaa ccc agt gct cat ttg gat cca gta aca tac caa ata att aga     4059
Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile Ile Arg
    1295                1300                1305

aga act cta aaa caa gca ttt gct gat tgc aca gta att ctc tgt gaa     4107
Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val Ile Leu Cys Glu
1310                1315                1320                1325
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cac agg ata gaa gca atg ctg gaa tgc caa caa ttt ttg gtc ata gaa     4155
His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe Leu Val Ile Glu
                1330                1335                1340

gag aac aaa gtg cgg cag tac gat tcc atc cag aaa ctg ctg aac gag     4203
Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu Asn Glu
            1345                1350                1355

agg agc ctc ttc cgg caa gcc atc agc ccc tcc gac agg gtg aag ctc     4251
Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser Asp Arg Val Lys Leu
        1360                1365                1370

ttt ccc cac cgg aac tca agc aag tgc aag tct aag ccc cag att gct     4299
Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln Ile Ala
    1375                1380                1385

gct ctg aaa gag gag aca gaa gaa gag gtg caa gat aca agg ctt tag     4347
Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln Asp Thr Arg Leu  *
1390                1395                1400


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<211> LENGTH: 4311
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
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<222> LOCATION: (133)...(4311)

<400> SEQUENCE: 8

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gcccgagaga cc atg cag agg tcg cct ctg gaa aag gcc agc gtt gtc tcc    171
              Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser
               1               5                  10

aaa ctt ttt ttc agc tgg acc aga cca att ttg agg aaa gga tac aga      219
Lys Leu Phe Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg
     15                  20                  25

cag cgc ctg gaa ttg tca gac ata tac caa atc cct tct gtt gat tct      267
Gln Arg Leu Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser
 30                  35                  40                  45

gct gac aat cta tct gaa aaa ttg gaa aga gaa tgg gat aga gag ctg      315
Ala Asp Asn Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu
                 50                  55                  60

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt      363
Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe
             65                  70                  75

ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc      411
Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val
         80                  85                  90

acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat      459
Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr
     95                  100                 105

gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata      507
Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile
110                 115                 120                 125

ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc      555
Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala
                130                 135                 140

att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt      603
Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe
            145                 150                 155

agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat      651
Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp
        160                 165                 170
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aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac      699
Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn
    175                 180                 185

aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct      747
Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro
190                 195                 200                 205

ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg      795
Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala
                210                 215                 220

tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag      843
Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln
            225                 230                 235

gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg      891
Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly
        240                 245                 250

aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc      939
Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile
    255                 260                 265

caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att      987
Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile
270                 275                 280                 285

gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat     1035
Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr
                290                 295                 300

gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg     1083
Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val
            305                 310                 315

gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc     1131
Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu
        320                 325                 330

cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg     1179
Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala
    335                 340                 345

gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt     1227
Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu
350                 355                 360                 365

gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag     1275
Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys
                370                 375                 380

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta     1323
Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val
            385                 390                 395

aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa     1371
Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys
        400                 405                 410

caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc     1419
Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe
    415                 420                 425

ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat     1467
Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn
430                 435                 440                 445

ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga     1515
Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly
                450                 455                 460

gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct     1563
Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro
            465                 470                 475

tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag     1611
Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln
        480                 485                 490
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ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt     1659
Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly
    495                 500                 505

gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa     1707
Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln
510                 515                 520                 525

cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt     1755
Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu
                530                 535                 540

gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct     1803
Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser
            545                 550                 555

tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct     1851
Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser
        560                 565                 570

cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc     1899
Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser
    575                 580                 585

tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct     1947
Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser
590                 595                 600                 605

aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa     1995
Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu
                610                 615                 620

ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag     2043
Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln
            625                 630                 635

cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt     2091
Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe
        640                 645                 650

agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc     2139
Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe
    655                 660                 665

tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa     2187
Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln
670                 675                 680                 685

tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att     2235
Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile
                690                 695                 700

ctc aat cca atc aac tct cac cga aag aca aca gca tcc aca cga aaa     2283
Leu Asn Pro Ile Asn Ser His Arg Lys Thr Thr Ala Ser Thr Arg Lys
            705                 710                 715

gtg tca ctg gcc cct cag gca aac ttg act gaa ctg gat ata tat tca     2331
Val Ser Leu Ala Pro Gln Ala Asn Leu Thr Glu Leu Asp Ile Tyr Ser
        720                 725                 730

aga agg tta tct caa gaa act ggc ttg gaa ata agt gaa gaa gat atg     2379
Arg Arg Leu Ser Gln Glu Thr Gly Leu Glu Ile Ser Glu Glu Asp Met
    735                 740                 745

gag agc ata cca gca gtg act aca tgg aac aca tac ctt cga tat att     2427
Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile
750                 755                 760                 765

act gtc cac aag agc tta att ttt gtg cta att tgg tgc tta gta att     2475
Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile
                770                 775                 780

ttt ctg gca gag gtg gct gct tct ttg gtt gtg ctg tgg ctc ctt gga     2523
Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly
            785                 790                 795

aac act cct ctt caa gac aaa ggg aat agt act cat agt aga aat aac     2571
Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn
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agc tat gca gtg att atc acc agc acc agt tcg tat tat gtg ttt tac     2619
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    815                 820                 825

att tac gtg gga gta gcc gac act ttg ctt gct atg gga ttc ttc aga     2667
Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg
830                 835                 840                 845

ggt cta cca ctg gtg cat act cta atc aca gtg tcg aaa att tta cac     2715
Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His
                850                 855                 860

cac aaa atg tta cat tct gtt ctt caa gca cct atg tca acc ctc aac     2763
His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn
            865                 870                 875

acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc aaa gat ata gca     2811
Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala
        880                 885                 890

att ttg gat gac ctt ctg cct ctt acc ata ttt gac ttc atc cag ttg     2859
Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu
    895                 900                 905

tta tta att gtg att gga gct ata gca gtt gtc gca gtt tta caa ccc     2907
Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro
910                 915                 920                 925

tac atc ttt gtt gca aca gtg cca gtg ata gtg gct ttt att atg ttg     2955
Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu
                930                 935                 940

aga gca tat ttc ctc caa acc tca cag caa ctc aaa caa ctg gaa tct     3003
Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser
            945                 950                 955

gaa ggc agg agt cca att ttc act cat ctt gtt aca agc tta aaa gga     3051
Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly
        960                 965                 970

cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac ttt gaa act ctg     3099
Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu
    975                 980                 985

ttc cac aaa gct ctg aat tta cat act gcc aac tgg ttc ttg tac ctg     3147
Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu
 990                 995                1000                1005

tca aca ctg cgc tgg ttc caa atg aga ata gaa atg att ttt gtc atc     3195
Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile
                1010                1015                1020

ttc ttc att gct gtt acc ttc att tcc att tta aca aca gga gaa gga     3243
Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly
            1025                1030                1035

gaa gga aga gtt ggt att atc ctg act tta gcc atg aat atc atg agt     3291
Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser
        1040                1045                1050

aca ttg cag tgg gct gta aac tcc agc ata gat gtg gat agc ttg atg     3339
Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met
    1055                1060                1065

cga tct gtg agc cga gtc ttt aag ttc att gac atg cca aca gaa ggt     3387
Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly
1070                1075                1080                1085

aaa cct acc aag tca acc aaa cca tac aag aat ggc caa ctc tcg aaa     3435
Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser Lys
                1090                1095                1100

gtt atg att att gag aat tca cac gtg aag aaa gat gac atc tgg ccc     3483
Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro
            1105                1110                1115

tca ggg ggc caa atg act gtc aaa gat ctc aca gca aaa tac aca gaa     3531
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Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr Glu
        1120                1125                1130

ggt gga aat gcc ata tta gag aac att tcc ttc tca ata agt cct ggc     3579
Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro Gly
    1135                1140                1145

cag agg gtg ggc ctc ttg gga aga act gga tca ggg aag agt act ttg     3627
Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr Leu
1150                1155                1160                1165

tta tca gct ttt ttg aga cta ctg aac act gaa gga gaa atc cag atc     3675
Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln Ile
                1170                1175                1180

gat ggt gtg tct tgg gat tca ata act ttg caa cag tgg agg aaa gcc     3723
Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys Ala
            1185                1190                1195

ttt gga gtg ata cca cag aaa gta ttt att ttt tct gga aca ttt aga     3771
Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe Arg
        1200                1205                1210

aaa aac ttg gat ccc tat gaa cag tgg agt gat caa gaa ata tgg aaa     3819
Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp Lys
    1215                1220                1225

gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa cag ttt cct ggg     3867
Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro Gly
1230                1235                1240                1245

aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc cta agc cat ggc     3915
Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His Gly
                1250                1255                1260

cac aag cag ttg atg tgc ttg gct aga tct gtt ctc agt aag gcg aag     3963
His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys
            1265                1270                1275

atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat cca gta aca tac     4011
Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr
        1280                1285                1290

caa ata att aga aga act cta aaa caa gca ttt gct gat tgc aca gta     4059
Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val
    1295                1300                1305

att ctc tgt gaa cac agg ata gaa gca atg ctg gaa tgc caa caa ttt     4107
Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe
1310                1315                1320                1325

ttg gtc ata gaa gag aac aaa gtg cgg cag tac gat tcc atc cag aaa     4155
Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln Lys
                1330                1335                1340

ctg ctg aac gag agg agc ctc ttc cgg caa gcc atc agc ccc tcc gac     4203
Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser Asp
            1345                1350                1355

agg gtg aag ctc ttt ccc cac cgg aac tca agc aag tgc aag tct aag     4251
Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser Lys
        1360                1365                1370

ccc cag att gct gct ctg aaa gag gag aca gaa gaa gag gtg caa gat     4299
Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln Asp
    1375                1380                1385

aca agg ctt tag                                                    4311
Thr Arg Leu  *
1390


<210> SEQ ID NO 9
<211> LENGTH: 1352
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 9
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Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
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            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700

Ile Asn Ser Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr
705                 710                 715                 720

Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile
                725                 730                 735

Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val
            740                 745                 750

Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr
        755                 760                 765

His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser
    770                 775                 780

Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala
785                 790                 795                 800

Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val
                805                 810                 815

Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro
            820                 825                 830

Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe
        835                 840                 845
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Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe
    850                 855                 860

Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val
865                 870                 875                 880

Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val
                885                 890                 895

Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu
            900                 905                 910

Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val
        915                 920                 925

Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro
    930                 935                 940

Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn
945                 950                 955                 960

Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu
                965                 970                 975

Met Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu
            980                 985                 990

Thr Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala
        995                 1000                1005

Met Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp
    1010                1015                1020

Val Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp
1025                1030                1035                1040

Met Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn
                1045                1050                1055

Gly Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys
            1060                1065                1070

Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr
        1075                1080                1085

Ala Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe
    1090                1095                1100

Ser Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser
1105                1110                1115                1120

Gly Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu
                1125                1130                1135

Gly Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln
            1140                1145                1150

Gln Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe
        1155                1160                1165

Ser Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp
    1170                1175                1180

Gln Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile
1185                1190                1195                1200

Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys
                1205                1210                1215

Val Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val
            1220                1225                1230

Leu Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu
        1235                1240                1245

Asp Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe
    1250                1255                1260
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Ala Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu
1265                1270                1275                1280

Glu Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr
                1285                1290                1295

Asp Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala
            1300                1305                1310

Ile Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser
        1315                1320                1325

Lys Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu
    1330                1335                1340

Glu Glu Val Gln Asp Thr Arg Leu
1345                1350


<210> SEQ ID NO 10
<211> LENGTH: 1428
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 10

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285
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Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700
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Ile Asn Ser Thr Leu Gln Ala Arg Arg Arg Gln Ser Val Leu Asn Leu
705                 710                 715                 720

Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His Arg Lys Thr Thr
                725                 730                 735

Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn Leu Thr Glu
            740                 745                 750

Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly Leu Glu Ile
        755                 760                 765

Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Cys Phe Phe Asp Asp
    770                 775                 780

Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr
785                 790                 795                 800

Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val
                805                 810                 815

Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu
            820                 825                 830

Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn
        835                 840                 845

Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe
    850                 855                 860

Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe
865                 870                 875                 880

Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu
                885                 890                 895

His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu
            900                 905                 910

Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile
        915                 920                 925

Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln
    930                 935                 940

Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln
945                 950                 955                 960

Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met
                965                 970                 975

Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu
            980                 985                 990

Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys
        995                 1000                1005

Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr
    1010                1015                1020

Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr
1025                1030                1035                1040

Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val
                1045                1050                1055

Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu
            1060                1065                1070

Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met
        1075                1080                1085

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

Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu
1105                1110                1115                1120

Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser
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               1125                1130                1135

Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp
            1140                1145                1150

Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr
        1155                1160                1165

Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro
    1170                1175                1180

Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr
1185                1190                1195                1200

Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln
                1205                1210                1215

Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys
            1220                1225                1230

Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe
        1235                1240                1245

Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp
    1250                1255                1260

Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro
1265                1270                1275                1280

Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His
                1285                1290                1295

Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala
            1300                1305                1310

Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr
        1315                1320                1325

Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr
    1330                1335                1340

Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln
1345                1350                1355                1360

Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln
                1365                1370                1375

Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser
            1380                1385                1390

Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser
        1395                1400                1405

Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln
    1410                1415                1420

Asp Thr Arg Leu
1425


<210> SEQ ID NO 11
<211> LENGTH: 1425
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 11

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60
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Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
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                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700

Ile Asn Ser Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu
705                 710                 715                 720

Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile His Arg Lys Thr
                725                 730                 735

Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn Leu Thr
            740                 745                 750

Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly Leu Glu
        755                 760                 765

Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Asp Met Glu Ser
    770                 775                 780

Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val
785                 790                 795                 800

His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu
                805                 810                 815

Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr
            820                 825                 830

Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr
        835                 840                 845

Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr
    850                 855                 860

Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu
865                 870                 875                 880

Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His His Lys
                885                 890                 895

Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn Thr Leu
            900                 905                 910
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Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu
        915                 920                 925

Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu
    930                 935                 940

Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro Tyr Ile
945                 950                 955                 960

Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu Arg Ala
                965                 970                 975

Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly
            980                 985                 990

Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly Leu Trp
        995                 1000                1005

Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His
    1010                1015                1020

Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr
1025                1030                1035                1040

Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe
                1045                1050                1055

Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly
            1060                1065                1070

Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu
        1075                1080                1085

Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met Arg Ser
    1090                1095                1100

Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly Lys Pro
1105                1110                1115                1120

Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser Lys Val Met
                1125                1130                1135

Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro Ser Gly
            1140                1145                1150

Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly
        1155                1160                1165

Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg
    1170                1175                1180

Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser
1185                1190                1195                1200

Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly
                1205                1210                1215

Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly
            1220                1225                1230

Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn
        1235                1240                1245

Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp Lys Val Ala
    1250                1255                1260

Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu
1265                1270                1275                1280

Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His Gly His Lys
                1285                1290                1295

Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu
            1300                1305                1310

Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile
        1315                1320                1325
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Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val Ile Leu
    1330                1335                1340

Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe Leu Val
1345                1350                1355                1360

Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu
                1365                1370                1375

Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser Asp Arg Val
            1380                1385                1390

Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln
        1395                1400                1405

Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln Asp Thr Arg
    1410                1415                1420

Leu
1425


<210> SEQ ID NO 12
<211> LENGTH: 1412
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 12

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270
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Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685
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Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700

Ile Asn Ser Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu
705                 710                 715                 720

Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile His Arg Lys Thr
                725                 730                 735

Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn Leu Thr
            740                 745                 750

Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly Leu Asp
        755                 760                 765

Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr
    770                 775                 780

Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val
785                 790                 795                 800

Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu
                805                 810                 815

Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn
            820                 825                 830

Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe
        835                 840                 845

Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe
    850                 855                 860

Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu
865                 870                 875                 880

His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu
                885                 890                 895

Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile
            900                 905                 910

Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln
        915                 920                 925

Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln
    930                 935                 940

Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met
945                 950                 955                 960

Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu
                965                 970                 975

Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys
            980                 985                 990

Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr
        995                 1000                1005

Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr
    1010                1015                1020

Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val
1025                1030                1035                1040

Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu
                1045                1050                1055

Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met
            1060                1065                1070

Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu
        1075                1080                1085

Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu
    1090                1095                1100

Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser
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1105                1110                1115                1120

Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp
                1125                1130                1135

Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr
            1140                1145                1150

Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro
        1155                1160                1165

Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr
    1170                1175                1180

Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln
1185                1190                1195                1200

Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys
                1205                1210                1215

Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe
            1220                1225                1230

Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp
        1235                1240                1245

Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro
    1250                1255                1260

Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His
1265                1270                1275                1280

Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala
                1285                1290                1295

Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr
            1300                1305                1310

Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr
        1315                1320                1325

Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln
    1330                1335                1340

Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln
1345                1350                1355                1360

Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser
                1365                1370                1375

Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser
            1380                1385                1390

Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln
        1395                1400                1405

Asp Thr Arg Leu
    1410


<210> SEQ ID NO 13
<211> LENGTH: 1411
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 13

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60
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Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
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                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700

Ile Asn Ser Thr Leu Gln Ala Arg Arg Arg Gln Ser Val Leu Asn Leu
705                 710                 715                 720

Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His Arg Lys Thr Thr
                725                 730                 735

Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn Leu Thr Glu
            740                 745                 750

Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly Leu Asp Met
        755                 760                 765

Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile
    770                 775                 780

Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile
785                 790                 795                 800

Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly
                805                 810                 815

Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn
            820                 825                 830

Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr
        835                 840                 845

Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg
    850                 855                 860

Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His
865                 870                 875                 880

His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn
                885                 890                 895

Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala
            900                 905                 910
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Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu
        915                 920                 925

Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro
    930                 935                 940

Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu
945                 950                 955                 960

Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser
                965                 970                 975

Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly
            980                 985                 990

Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu
        995                 1000                1005

Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu
    1010                1015                1020

Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile
1025                1030                1035                1040

Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly
                1045                1050                1055

Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser
            1060                1065                1070

Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met
        1075                1080                1085

Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly
    1090                1095                1100

Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser Lys
1105                1110                1115                1120

Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro
                1125                1130                1135

Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr Glu
            1140                1145                1150

Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro Gly
        1155                1160                1165

Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr Leu
    1170                1175                1180

Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln Ile
1185                1190                1195                1200

Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys Ala
                1205                1210                1215

Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe Arg
            1220                1225                1230

Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp Lys
        1235                1240                1245

Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro Gly
    1250                1255                1260

Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His Gly
1265                1270                1275                1280

His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys
                1285                1290                1295

Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr
            1300                1305                1310

Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val
        1315                1320                1325
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Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe
    1330                1335                1340

Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln Lys
1345                1350                1355                1360

Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser Asp
                1365                1370                1375

Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser Lys
            1380                1385                1390

Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln Asp
        1395                1400                1405

Thr Arg Leu
    1410


<210> SEQ ID NO 14
<211> LENGTH: 1404
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 14

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285
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Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700
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Ile Asn Ser Ile Arg Lys Phe Ser Ile Val Gln Lys Thr Pro Leu Gln
705                 710                 715                 720

Met Asn Gly Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu
                725                 730                 735

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

Ser Val Ile Ser Thr Gly Pro Asp Met Glu Ser Ile Pro Ala Val Thr
        755                 760                 765

Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile
    770                 775                 780

Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala
785                 790                 795                 800

Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys
                805                 810                 815

Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr
            820                 825                 830

Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp
        835                 840                 845

Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr
    850                 855                 860

Leu Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu His Ser Val
865                 870                 875                 880

Leu Gln Ala Pro Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile
                885                 890                 895

Leu Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro
            900                 905                 910

Leu Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala
        915                 920                 925

Ile Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val
    930                 935                 940

Pro Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr
945                 950                 955                 960

Ser Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe
                965                 970                 975

Thr His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe
            980                 985                 990

Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu
        995                 1000                1005

His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln
    1010                1015                1020

Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe
1025                1030                1035                1040

Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile
                1045                1050                1055

Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn
            1060                1065                1070

Ser Ser Ile Asp Val Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe
        1075                1080                1085

Lys Phe Ile Asp Met Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys
    1090                1095                1100

Pro Tyr Lys Asn Gly Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser
1105                1110                1115                1120

His Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val
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               1125                1130                1135

Lys Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu
            1140                1145                1150

Asn Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly
        1155                1160                1165

Arg Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu
    1170                1175                1180

Leu Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser
1185                1190                1195                1200

Ile Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys
               1205                1210                1215

Val Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu
            1220                1225                1230

Gln Trp Ser Asp Gln Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu
        1235                1240                1245

Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val
    1250                1255                1260

Asp Gly Gly Cys Val Leu Ser His Gly His Lys Gln Leu Met Cys Leu
1265                1270                1275                1280

Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro
               1285                1290                1295

Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu
            1300                1305                1310

Lys Gln Ala Phe Ala Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile
        1315                1320                1325

Glu Ala Met Leu Glu Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys
    1330                1335                1340

Val Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu
1345                1350                1355                1360

Phe Arg Gln Ala Ile Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His
               1365                1370                1375

Arg Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys
            1380                1385                1390

Glu Glu Thr Glu Glu Glu Val Gln Asp Thr Arg Leu
        1395                1400


<210> SEQ ID NO 15
<211> LENGTH: 1404
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 15

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
               85                  90                  95
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Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
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        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700

Ile Asn Ser His Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu
705                 710                 715                 720

Ala Pro Gln Ala Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu
                725                 730                 735

Ser Gln Glu Thr Gly Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp
            740                 745                 750

Leu Lys Glu Cys Phe Phe Asp Asp Met Glu Ser Ile Pro Ala Val Thr
        755                 760                 765

Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile
    770                 775                 780

Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala
785                 790                 795                 800

Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys
                805                 810                 815

Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr
            820                 825                 830

Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp
        835                 840                 845

Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr
    850                 855                 860

Leu Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu His Ser Val
865                 870                 875                 880

Leu Gln Ala Pro Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile
                885                 890                 895

Leu Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro
            900                 905                 910

Leu Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala
        915                 920                 925

Ile Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val
    930                 935                 940
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Pro Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr
945                 950                 955                 960

Ser Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe
                965                 970                 975

Thr His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe
            980                 985                 990

Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu
        995                 1000                1005

His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln
    1010                1015                1020

Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe
1025                1030                1035                1040

Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile
                1045                1050                1055

Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn
            1060                1065                1070

Ser Ser Ile Asp Val Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe
        1075                1080                1085

Lys Phe Ile Asp Met Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys
    1090                1095                1100

Pro Tyr Lys Asn Gly Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser
1105                1110                1115                1120

His Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val
                1125                1130                1135

Lys Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu
            1140                1145                1150

Asn Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly
        1155                1160                1165

Arg Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu
    1170                1175                1180

Leu Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser
1185                1190                1195                1200

Ile Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys
                1205                1210                1215

Val Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu
            1220                1225                1230

Gln Trp Ser Asp Gln Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu
        1235                1240                1245

Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val
    1250                1255                1260

Asp Gly Gly Cys Val Leu Ser His Gly His Lys Gln Leu Met Cys Leu
1265                1270                1275                1280

Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro
                1285                1290                1295

Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu
            1300                1305                1310

Lys Gln Ala Phe Ala Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile
        1315                1320                1325

Glu Ala Met Leu Glu Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys
    1330                1335                1340

Val Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu
1345                1350                1355                1360
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Phe Arg Gln Ala Ile Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His
                1365                1370                1375

Arg Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys
            1380                1385                1390

Glu Glu Thr Glu Glu Glu Val Gln Asp Thr Arg Leu
        1395                1400


<210> SEQ ID NO 16
<211> LENGTH: 1392
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 16

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe
 1               5                  10                  15

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu
            20                  25                  30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn
        35                  40                  45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys
    50                  55                  60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg
65                  70                  75                  80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala
                85                  90                  95

Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp
            100                 105                 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys
        115                 120                 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly
    130                 135                 140

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile
145                 150                 155                 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser
                165                 170                 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp
            180                 185                 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val
        195                 200                 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe
    210                 215                 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu
225                 230                 235                 240

Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser
                245                 250                 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val
            260                 265                 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu
        275                 280                 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr
    290                 295                 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu
305                 310                 315                 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile
                325                 330                 335
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Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg
            340                 345                 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile
        355                 360                 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu
    370                 375                 380

Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe
385                 390                 395                 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn
                405                 410                 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn
            420                 425                 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile
        435                 440                 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys
    450                 455                 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly
465                 470                 475                 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp
                485                 490                 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr
            500                 505                 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu
        515                 520                 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly
    530                 535                 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg
545                 550                 555                 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly
                565                 570                 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys
            580                 585                 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu
        595                 600                 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu Gly Ser Ser
    610                 615                 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe
625                 630                 635                 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu
                645                 650                 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu
            660                 665                 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys
        675                 680                 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro
    690                 695                 700

Ile Asn Ser His Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu
705                 710                 715                 720

Ala Pro Gln Ala Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu
                725                 730                 735

Ser Gln Glu Thr Gly Leu Glu Ile Ser Glu Glu Asp Met Glu Ser Ile
            740                 745                 750
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Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His
        755                 760                 765

Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala
    770                 775                 780

Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro
785                 790                 795                 800

Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala
                805                 810                 815

Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val
            820                 825                 830

Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro
        835                 840                 845

Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His His Lys Met
    850                 855                 860

Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn Thr Leu Lys
865                 870                 875                 880

Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp
                885                 890                 895

Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu Leu Leu Ile
            900                 905                 910

Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe
        915                 920                 925

Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr
    930                 935                 940

Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg
945                 950                 955                 960

Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr
                965                 970                 975

Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys
            980                 985                 990

Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu
        995                 1000                1005

Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile
    1010                1015                1020

Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg
1025                1030                1035                1040

Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu Gln
                1045                1050                1055

Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met Arg Ser Val
            1060                1065                1070

Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly Lys Pro Thr
        1075                1080                1085

Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser Lys Val Met Ile
    1090                1095                1100

Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly
1105                1110                1115                1120

Gln Met Thr Val Lys Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly Asn
                1125                1130                1135

Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg Val
            1140                1145                1150

Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser Ala
        1155                1160                1165

Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly Val
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    1170                1175                1180

Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly Val
1185                1190                1195                1200

Ile Pro Gln Lys Val Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn Leu
                1205                1210                1215

Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu Ile Trp Lys Val Ala Asp
            1220                1225                1230

Glu Val Gly Leu Arg Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp
        1235                1240                1245

Phe Val Leu Val Asp Gly Gly Cys Val Leu Ser His Gly His Lys Gln
    1250                1255                1260

Leu Met Cys Leu Ala Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu
1265                1270                1275                1280

Leu Asp Glu Pro Ser Ala His Leu Asp Pro Val Thr Tyr Gln Ile Ile
                1285                1290                1295

Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp Cys Thr Val Ile Leu Cys
            1300                1305                1310

Glu His Arg Ile Glu Ala Met Leu Glu Cys Gln Gln Phe Leu Val Ile
        1315                1320                1325

Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu Asn
    1330                1335                1340

Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro Ser Asp Arg Val Lys
1345                1350                1355                1360

Leu Phe Pro His Arg Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln Ile
                1365                1370                1375

Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu Val Gln Asp Thr Arg Leu
            1380                1385                1390
```

We claim:

1. An isolated and purified DNA molecule having the sequence set forth in SEQ ID NO:2.

2. A vector comprising the DNA molecule of claim **1**.

3. The vector of claim **2**, wherein the vector is adeno-associated virus (AAV).

4. The vector of claim **3**, wherein the vector is selected from the group consisting of AAV type 5 or AAV type 6.

5. The vector of claim **2**, wherein the vector is adenovirus.

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