



US007339046B2

(12) **United States Patent**  
**Welsh et al.**

(10) **Patent No.:** **US 7,339,046 B2**  
(45) **Date of Patent:** **Mar. 4, 2008**

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

(75) Inventors: **Michael J. Welsh**, Riverside, IA (US);  
**Lynda S. Ostedgaard**, Iowa City, IA (US); **Joseph Zabner**, Iowa City, IA (US)

(73) Assignee: **University of Iowa Research Foundation**, Iowa City, IA (US)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 562 days.

(21) Appl. No.: **10/367,507**

(22) Filed: **Feb. 14, 2003**

(65) **Prior Publication Data**

US 2003/0235885 A1 Dec. 25, 2003

**Related U.S. Application Data**

(60) Provisional application No. 60/358,074, filed on Feb. 19, 2002.

(51) **Int. Cl.**  
**A61K 38/16** (2006.01)  
**C07H 21/04** (2006.01)

(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.

(56) **References Cited**

**OTHER PUBLICATIONS**

Welsh, M. et al, "Cystic Fibrosis", (1995), *McGraw-Hill Health Professions Division*, 3: (3799-3839).

Karp PH, Moninger TO, Weber SP, Nesselhauf TS, Launspach JL, Zabner J, Welsh MJ. An in vitro model of differentiated human airway epithelia. Methods for establishing primary cultures. *Methods Mol Biol* 2002;188:115-37.

Baldursson O, Ostedgaard LS, Rokhlina T, Cotton JF, Welsh MJ. Cystic fibrosis transmembrane conductance regulator C1-channels with R domain deletions and translocations show phosphorylation-dependent and independent activity. *J Biol Chem* 2001;276(3):1904-1910.

Davies JC, Geddes DM, Alton EW. Gene therapy for cystic fibrosis. *J Gene Med* 2001;3(5):409-417.

Halbert CL, Allen JM, Miller AD. Adeno-associated virus type 6 (AAV6) vectors mediate efficient transduction of airway epithelial cells in mouse lungs compared to that of AAV2 vectors. *J Virol* 2001;75(14):6615-6624.

Nagel G, Szellas T, Riordan JR, Friedrich T, Hartung K. Non-specific activation of the epithelial sodium channel by the CFTR chloride channel. *EMBO Rep* 2001;2(3):249-254.

Ostedgaard LS, Baldursson O, Welsh MJ. Regulation of the cystic fibrosis transmembrane conductance regulator C1-channel by its R domain. *J Biol Chem* 2001;276(11):7689-7692.

Walters RW, Yi SM, Keshavjee S, Brown KE, Welsh MJ, Chiorini JA, Zabner J. Binding of adeno-associated virus type 5 to 2,3-linked sialic acid is required for gene transfer. *J Biol Chem* 2001;276(23):20610-20616.

Athanasopoulos T, Fabb S, Dickson G. Gene therapy vectors based on adeno-associated virus: characteristics and applications to acquired and inherited diseases (review). *Int J Mol Med* 2000;6(4):363-375.

Carter PJ, Samulski RJ. Adeno-associated viral vectors as gene delivery vehicles. *Int J Mol Med* 2000;6(1):17-27.

Csanady L, Chan KW, Seto-Young D, Kopsco DC, Nairn AC, Gadsby DC. Severed channels probe regulation of gating of cystic fibrosis transmembrane conductance regulator by its cytoplasmic domains. *J Gen Physiol* 2000;116:477-500.

Ma J. Stimulatory and inhibitory functions in the R domain of CFTR chlorine channel. *News Physiol Sci* 2000;154-158.

Ostedgaard LS, Baldursson O, Vermeer DW, Welsh MJ. A functional R domain from cystic fibrosis transmembrane conductance regulator is predominantly unstructured in solution. *Proc Natl Acad Sci U.S.A.* 2001;97(10):5657-5662.

Welsh MJ et al. The Metabolic and Molecular Basis of Inherited Disease. eds. Scriver, Beaudet, Sly, Valle, Childs & Vogelstein 2000;(McGraw-Hill, New York) pp. 5121-5189.

Xie J, Zhao J, Davis PB, Ma J. Conformation, independent of charge, in the R domain affects cystic fibrosis transmembrane conductance regulator channel openings. *Biophys J* 2000;78(3):1293-1305.

Zabner J, Seiler M, Walters R, Kotin RM, Fulgeras W, Davidson BL, Chiorini JA. Adeno-associated virus type 5 (AAV5) but not AAV2 binds to the apical surfaces of airway epithelia and facilitates gene transfer. *J Virol* 2000;74(8):3852-3858.

Chang XB, Cui L, Hou YX, Jensen TJ, Aleksandrov AA, Mengos A, Riordan JR. Removal of multiple arginine-framed trafficking signals overcomes misprocessing of delta F508 CFTR present in most patients with cystic fibrosis. *Mol Cell* 1999;4(1):137-142.

Flotte TR. Gene therapy for cystic fibrosis. *Curr Opin Mol Ther*, 1999;1(4):510-516.

Gadsby DC, Nairn AC. Control of CFTR channel gating by phosphorylation and nucleotide hydrolysis. *Physiol Rev* 1999;79(1):S77-S107.

Ostedgaard LS, Zeiher B, Welsh MJ. Processing of CFTR bearing the P574H mutation differs from wild-type and deltaF508-CFTR. *J Cell Sci*, 1999;112(Pt 13):2091-2098.

Schwiebert EM, Benos DJ, Egan ME, Stutts MJ, Guggino WB. CFTR is a conductance regulator as well as a chloride channel. *Physiol Rev* 1999;79(1 Suppl):S145-166.

Sheppard DN, Welsh MJ. Structure and function of the CFTR chloride channel. *Physiol Rev* 1999;79(1 Suppl):S23-S45.

(Continued)

*Primary Examiner*—Gary B. Nickol  
*Assistant Examiner*—Nirmal S. Basi  
(74) *Attorney, Agent, or Firm*—Arent Fox LLP

(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)**

## OTHER PUBLICATIONS

- Vankeerberghen A, Lin W, Jaspers M, Cuppens H, Nilius B, Cassiman JJ. Functional characterization of the CFTR R domain using CFTR/MDR1 hybrid and deletion constructs. *Biochemistry* 1999;38(45):14988-14998.
- Walters RW, Grunst T, Bergelson JM, Finberg RW, Welsh MJ, Zabner J. Basolateral localization of fiber receptors limits adenovirus infection from the apical surface of airway epithelia. *J Biol Chem* 1999;274(15):10219-10226.
- Fasbender A, Lee JH, Walters RW, Moniger TO, Zabner J, Welsh MJ. Incorporation of adenovirus in calcium phosphate precipitates enhances gene transfer to airway epithelia in vitro and in vivo. *J Clin Invest* 1998;102(1):184-193.
- Summerford C, Samulski RJ. Membrane-associated heparan sulfate proteoglycan is a receptor for adeno-associated virus type 2 virions. *J Virol* 1998;72(2):1438-1445.
- Vankeerberghen A, Wei L, Jaspers M, Cassiman JJ, Nilius B, Cuppens H. Characterization of 19 disease-associated missense mutations in the regulatory domain of the cystic fibrosis transmembrane conductance regulator. *Hum Mol Genet* 1998;7(11):1761-1769.
- Zabner J, Smith JJ, Karp PH, Widdicombe JH, Welsh MJ. Loss of CFTR chloride channels alters salt absorption by cystic fibrosis airway epithelia in vitro. *Mol Cell* 1998;2(3):397-403.
- Zhang L, Wang D, Fischer H, Fan PD, Widdicombe JH, Kan YW, Dong JY. Efficient expression of CFTR function with adeno-associated virus vectors that carry shortened CFTR genes. *Proc Natl Acad Sci U S A* 1998;95(17):10158-10163.
- Ma J, Zhao J, Drumm ML, Xie J, Davis PB. Function of the R domain in the cystic fibrosis transmembrane conductance regulator chloride channel. *J Biol Chem* 1997;272:28133-28141.
- Winter MC, Welsh MJ. Stimulation of CFTR activity by its phosphorylated R domain. *Nature* 1997;389(6648):294-296.
- Wilkinson DJ, Strong TV, Mansoura MK, Wood DL, Smith SS, Collins FS, Dawson DC. CFTR activation: additive effects of stimulatory and inhibitory phosphorylation sites in the R domain. *Am J Physiol* 1997;273(1 Pt):L127-L133.
- Dong JY, Fan PD, Frizzell RA. Quantitative analysis of the packaging capacity of recombinant adeno-associated virus. *Hum Gene Ther* 1996;7(17):2101-2112.
- Carson MR, Travis SM, Welsh MJ. The two nucleotide-binding domains of cystic fibrosis transmembrane conductance regulator (CFTR) have distinct functions in controlling channel activity. *J Biol Chem* 1995;270(4):1711-1717.
- Johnson LG, Boyles SE, Wilson J, Boucher RC. Normalization of raised sodium absorption and raised calcium-mediated chloride secretion by adenovirus-mediated expression of cystic fibrosis transmembrane conductance regulator in primary human cystic fibrosis airway epithelial cells. *J Clin Invest* 1995;95(3):1377-1382.
- Phelps SF, Hauser MA, Cole NM, Rafael JA, Hinkle RT, Faulkner JA, Chamberlain JS. Expression of full-length and truncated dystrophin mini-genes in transgenic mdx mice. *Hum Mol Genet* 1995;4(8):1251-1258.
- Zeiber BG, Eichwald E, Zabner J, Smith JJ, Puga AP, McCray PB, Jr., Capocchi MR, Welsh MJ, Thomas KR. A mouse model for the delta F508 allele of cystic fibrosis. *J Clin Invest* 1995;96(4):2051-2064.
- Boucher RC. Human airway ion transport. Part One *Am J Respir Crit Care Med* 1994;150(1):271-281.
- Flotte TR, Afione SA, Solow R, Drumm ML, Markakis D, Guggino WB, Zeitlin PL, Carter BJ. Expression of the cystic fibrosis transmembrane conductance regulator from a novel adeno-associated virus promoter. *J Biol Chem* 1993;268(5):3781-3790.
- Rich DP, Gregory RJ, Cheng SH, Smith AE, Welsh MJ. Effect of deletion mutations on the function of CFTR chloride channels. *Receptors Channels* 1993;1:221-232.
- Blobel CP, Wolfsberg TG, Turck CW, Myles DG, Primakoff P, White JM. A potential fusion peptide and an integrin ligand domain in a protein active in sperm-egg fusion. *Nature* 1992;356(6366):248-252.
- Muzyczka N. Use of adeno-associated virus as a general transduction vector for mammalian cells. *Curr Topics Microbiol Immunol* 1992;158:97-129.
- Rosenfeld MA, Yoshimura K, Trapnell BC, Yoneyama K, Rosenthal ER, Dalemans W, Fukayama M, Bargon J, Stier LE, Stratford-Perricaudet L et al. In vivo transfer of the human cystic fibrosis transmembrane conductance regulator gene to the airway epithelium. *Cell* 1992;68(1):143-155.
- Tilly BC, Winter MC, Ostedgaard LS, O'Riordan C, Smith AE, Welsh MJ. Cyclic AMP-dependent protein kinase activation of cystic fibrosis transmembrane conductance regulator chloride channels in planar lipid bilayers. *J Biol Chem* 1992;267(14):9470-9473.
- Curiel DT, Agarwal S, Wagner E, Cotton M. Adenovirus enhancement of transferrin-polylysine-mediated gene delivery. *Proc Natl Acad Sci USA*, 1991;88(19):8850-8854.
- Hazinski TA, Ladd PA, DeMatteo CA. Localization and induced expression of fusion genes in the rat lung. *Am J Respir Cell Mol Biol* 1991;4(3):206-209.
- Rich DP, Gregory RJ, Anderson MP, Manavalan P, Smith AE, Welsh MJ. Effect of deleting the R domain on CFTR-generated chloride channels. *Science* 1991;253(5016):205-207.
- Rosenfeld MA, Siegfried W, Yoshimura K, Yoneyama K, Fukayama M, Stier LE, Paakko PK, Gilardi P, Stratford-Perricaudet LD, Perricaudet M et al. Adenovirus-mediated transfer of a recombinant alpha 1-antitrypsin gene to the lung epithelium in vivo. *Science* 1991;252(5004):431-434.
- Cheng SH, Gregory RJ, Marshall J, Paul S, Souza DW, White GA, O'Riordan CR, Smith AE. Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. *Cell* 1990;63(4):827-834.
- Miller AD. Progress toward human gene therapy. *Blood* 1990;76(2):271-278.
- Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, Felgner PL. Direct gene transfer into mouse muscle in vivo. *Science* 1990;247(4949 Pt 1):1465-1468.
- Felgner PL, Ringold GM. Cationic liposome-mediated transfection. *Nature* 1989;337(6205):387-388.
- Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989;245(4922):1066-1073.
- Berkner KL. Development of adenovirus vectors for the expression of heterologous genes. *BioTechniques* 1988;6(7):616-629.
- Wu GY, Wu CH. Receptor-mediated gene delivery and expression in vivo. *J Biol Chem* 1988;263(29):14621-14624.
- Green M, Wold WS, Mackey JK, Rigden P. Analysis of human tonsil and cancer DNAs and RNAs for DNA sequences of group C (serotypes 1, 2, 5 and 6) human adenoviruses. *Proc Natl Acad Sci USA* 1979;76(12):6606-6610.
- Schwartz AR, Togo Y, Hornick RB. Clinical evaluation of live, oral types 1, 2 and 5 adenovirus vaccines. *Am Rev Respir Dis* 1974;109(2):233-238.

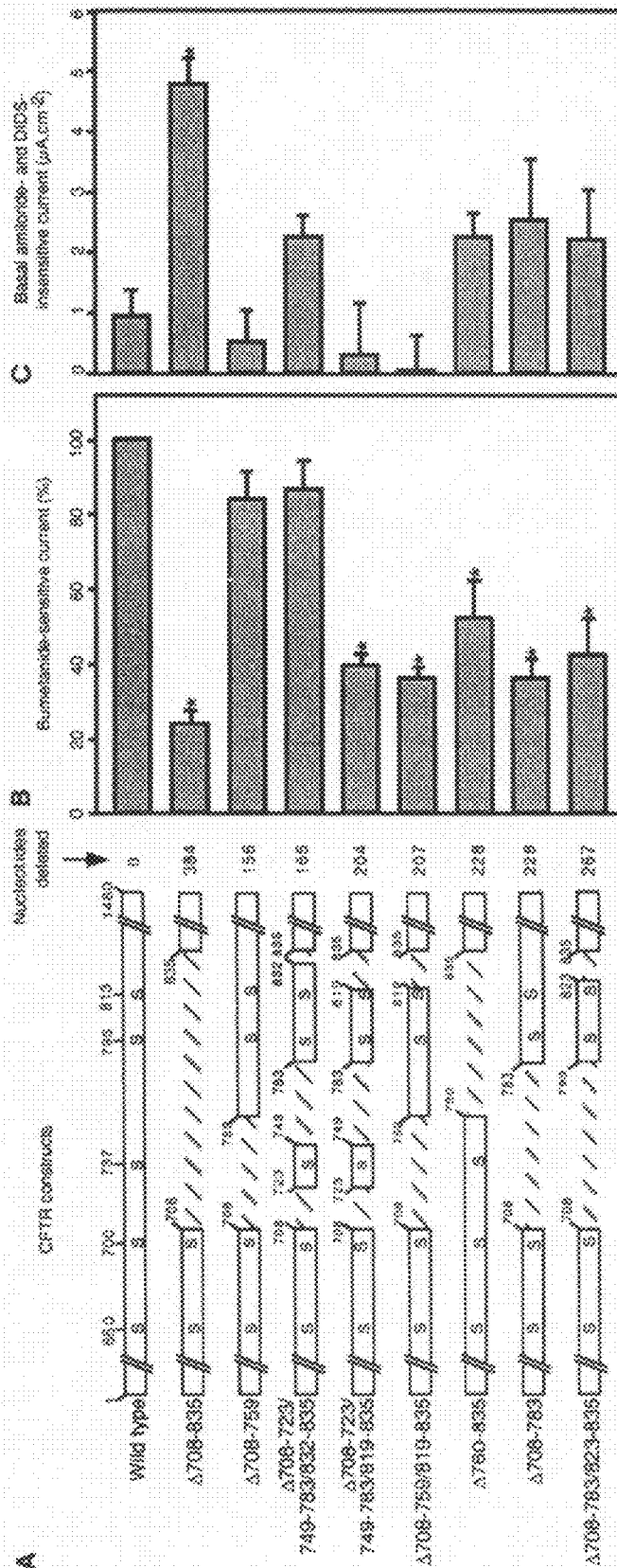


Figure 1

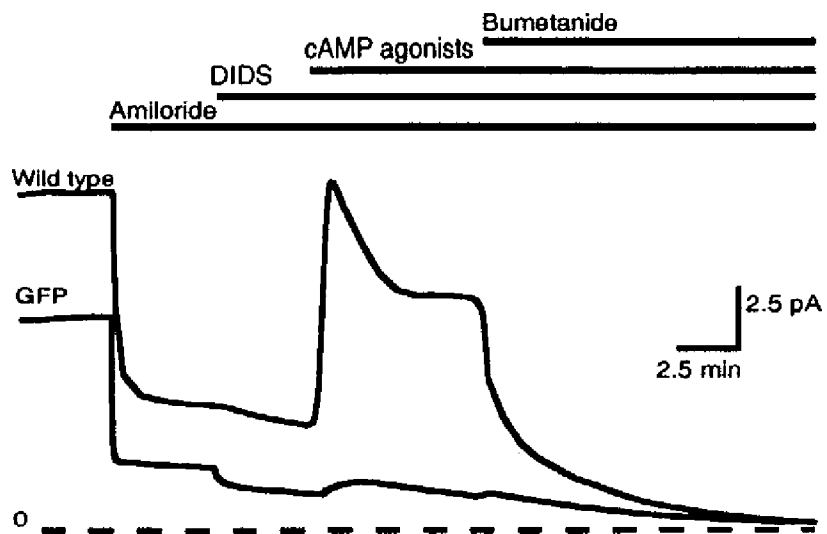


Figure 2

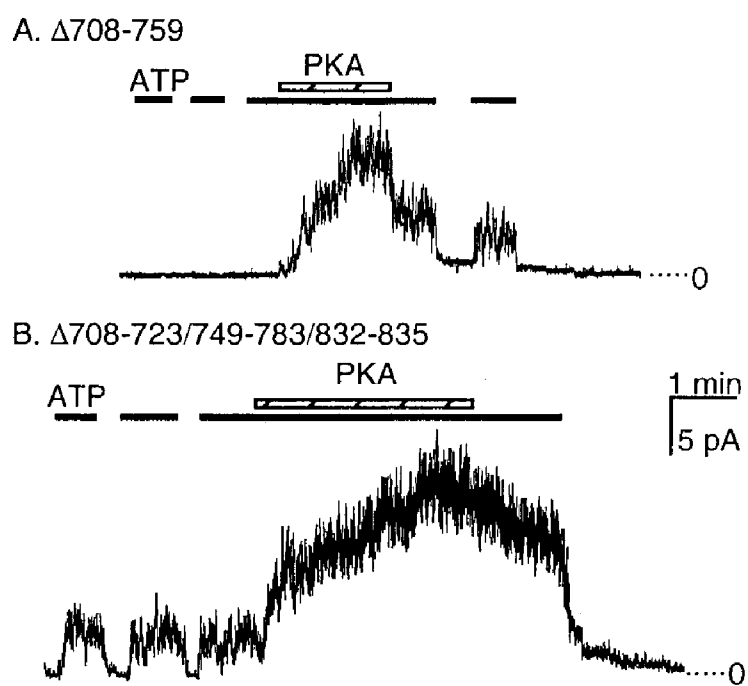


Figure 3

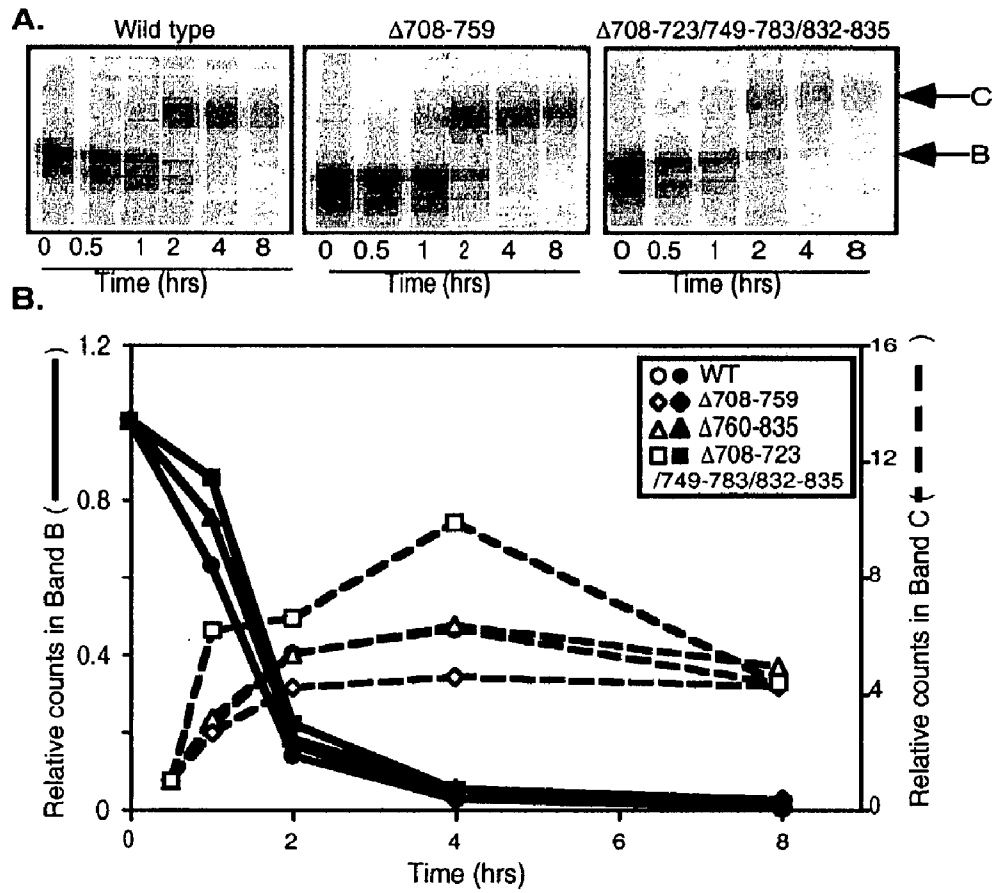


Figure 4

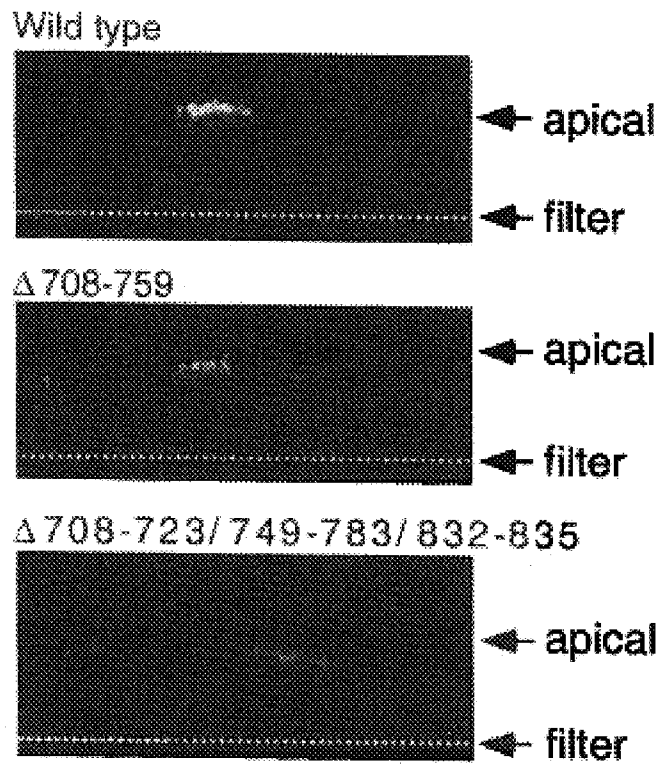


Figure 5

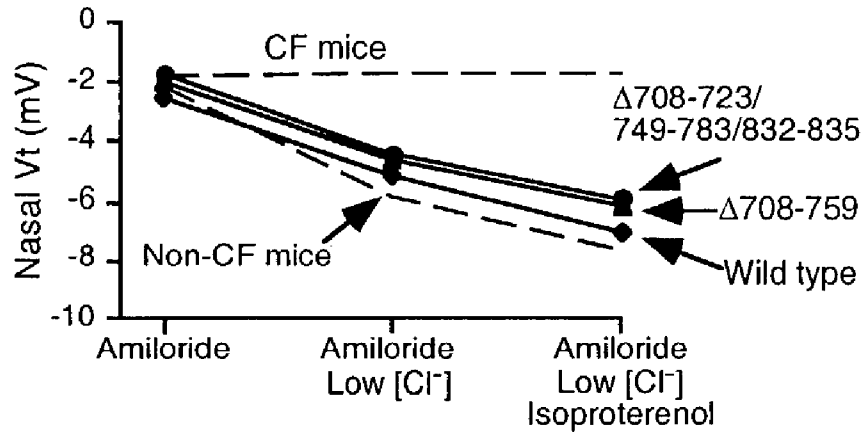


Figure 6



## 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<sup>-</sup> channel. Welsh et al., *The Metabolic and Molecular Basis of 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 Duchennes 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, *Physiol. 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<sup>-</sup> 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, *Physiol. Rev.* 79:S77-S107; and Ma, 2000, *News Physiol. Sci.* 15:154-158) to provide a partially deleted CFTR capable of forming Cl<sup>-</sup> 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<sup>-</sup> current in CF epithelia (see Examples below). In addition, the CFTR protein comprising a partially deleted R domain corrects the Cl<sup>-</sup> 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<sup>-</sup> 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  $\Delta 708-759$ ,  $\Delta 708-723/749-783/832-835$  and  $\Delta 760-835$ .

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. 1A shows a graphic representation of exemplary embodiments of CFTR proteins of the present invention; 1B shows bumetanide-sensitive short-circuit current in well-differentiated CF epithelia expressing the exemplary proteins shown in panel A; 1C 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  $\Delta 708-759$ , and 3B is  $\Delta 708-723/749-783/832-835$ ;

FIG. 4A depicts gels showing CFTR at indicated time after pulse with <sup>35</sup>S-methionine and showing the disappearance of band B (immature) and band C (mature); 4B 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](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-

appropriate 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, metallothionein 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 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<sup>-</sup> current. As used herein, "low constitutive Cl<sup>-</sup> current" means an amount of Cl<sup>-</sup> current as determined in patch-clamp studies (described by Baldursson et al., 2001, *J. Biol. Chem.* 276:1904-1910) which is less than 2 μA.cm<sup>-2</sup>. In one embodiment, the CFTR having low constitutive Cl<sup>-</sup> 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* 267:9470-73). A preferred method of purification involves first solubilizing the protein in the presence of a non-denaturing 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 hemagglutinin 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 full 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 mechanism 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  $\Delta 708-835$ , 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. 1A shows the eight variants constructed which include,  $\Delta 708-835$  (SEQ ID NO:9),  $\Delta 708-759$  (SEQ ID NO:10),  $\Delta 708-723/749-783/832-835$  (SEQ ID NO:11),  $\Delta 708-723/$

749-783/819-835 (SEQ ID NO:12),  $\Delta 708-759/819-835$  (SEQ ID NO:13),  $\Delta 760-835$  (SEQ ID NO:14),  $\Delta 708-783$  (SEQ ID NO:15), and  $\Delta 708-783/823-835$  (SEQ ID NO:16). FIG. 1A indicates the deletions by crosshatching. Serines that are phosphorylated *in vivo* are indicated in FIG. 1A 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. 1A.

### 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  $\gamma\text{-}^{32}\text{P}\text{-ATP}$  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  $^{35}\text{S}\text{-methionine}$ , and pulse-chase studies carried out as described previously (Ost-edgaard, 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. 4A&B show that two representative CFTR proteins of the present invention comprising partially deleted R domains, namely  $\Delta 708-759$  and  $\Delta 708-723/749-783/832-835$ , demonstrate similar disappearance of band B and appearance of band C as wild type. FIG. 4A shows the appearance in a gel and FIG. 4B 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 ( $\Delta F508/\Delta F508$  or  $\Delta F508$ /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).

## 11

## 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<sub>2</sub>, 1.2 mM CaCl<sub>2</sub>, 2.4 mM K<sub>2</sub>PO<sub>4</sub>, 0.6 mM KH<sub>2</sub>PO<sub>4</sub>, 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<sup>-4</sup> M), mucosal 4,4'-diisothiocyanato-stilbene-2,2'-disulfonic acid (DIDS, 10<sup>-4</sup> M); the cAMP agonists mucosal forskolin (10<sup>-5</sup> M) plus 3-isobutyl-2-methylxanthine (IBMX, 10<sup>-4</sup> M), and submucosal bumetanide (10<sup>-4</sup> M) were sequentially added (see FIG. 2). For a limited number of studies, epithelia were treated with forskolin (10<sup>-5</sup> M) and IBMX (10<sup>-4</sup> 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 (Zeiber et al., 1995, *J. Clin. Invest.* 96:2051-2064). Mice were lightly anesthetized in a halothane chamber. Adenovirus vectors (5×10<sup>9</sup> 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 (Zeiber 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<sub>2</sub>PO<sub>4</sub>, 0.6 K<sub>2</sub>HPO<sub>4</sub>, 1.2 CaCl<sub>2</sub>, 1.2 MgCl<sub>2</sub>, 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-

## 12

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. 1A 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<sup>-</sup> 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<sup>+</sup> channels, hyperpolarize the apical membrane, and thereby generate a driving force for Cl<sup>-</sup> secretory currents; b) DIDS to inhibit DIDS-sensitive apical Cl<sup>-</sup> channels; c) cAMP agonists to activate CFTR; and d) bumetanide to inhibit basolateral Cl<sup>-</sup> co-transport. Under these conditions, bumetanide-sensitive current provides the most accurate assessment of CFTR-dependent transepithelial Cl<sup>-</sup> transport.

All the CFTR variants produced transepithelial Cl<sup>-</sup> currents (FIG. 1B). The data in FIG. 1B 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 μA.cm<sup>-2</sup>. The asterisks in FIG. 1B 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. 1B, the Δ708-835 variant generated the least Cl<sup>-</sup> 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. 1B). The other variants produced intermediate levels of Cl<sup>-</sup> current (FIG. 1B).

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<sup>+</sup> 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<sup>+</sup> current. However, in the present invention, amiloride-inhibited current is influenced not only by the activity of epithelial Na<sup>+</sup> channels, but also by the basal Cl<sup>-</sup> 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<sup>-</sup> 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<sup>+</sup> 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<sup>-</sup> channel activity. Then the current remaining after treatment with amiloride and DIDS, but before addition of cAMP agonists was measured, as shown in FIG. 1C, and FIG. 2). In FIG. 1C, 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. 1C 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<sup>-</sup> 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<sup>-</sup> 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. 1C, FIG. 3 shows that Δ708-723/749-783/832-835, but not Δ708-759 generated constitutive current. Specifically, FIG. 3A shows that Δ708-759 showed no current before phosphorylation with PKA and FIG. 3B 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<sup>-</sup> flow (Welsh et al., 2000, *The Metabolic and Molecular Basis of Inherited Disease*, eds. Scriver, Beaudet, Sly, Valle, Childs & Vogelstein (McGraw-Hill, New York) pp 5121-5189); an apical location is critical for its function in transepithelial Cl<sup>-</sup> 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<sup>-</sup> current in human airway epithelia. Epithelia were treated with amiloride to inhibit Na<sup>+</sup> channels and then Vt in response to perfusion was measured with solutions containing a low Cl<sup>-</sup> 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<sup>-</sup> 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<sup>-</sup> current. In contrast, Δ708-723/749-783/832-835 and Δ708-759/819-835 had greater, but still low, basal Cl<sup>-</sup> currents than wild type and showed constitutive Cl<sup>-</sup> current when examined in patch-clamp studies.

## 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<sup>-</sup> 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<sup>-</sup> 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<sup>-</sup> 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<sup>-</sup> 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).

## SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 16

<210> SEQ ID NO 1

<211> LENGTH: 4191

<212> TYPE: DNA

<213> ORGANISM: homo sapiens

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (133)...(4191)

<400> SEQUENCE: 1

```

aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca      60
gagtagtagg tctttggcat taggagcttg agcccagacg gccttagcag ggaccccagc      120
gcccagagaga cc atg cag agg tgc 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

```



-continued

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	cgf	ggt	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	ggt	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	ggt	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	ggt	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

-continued

---

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 Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys 400 405 410	1371
caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe 415 420 425	1419
ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn 430 435 440 445	1467
ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly 450 455 460	1515
gca gcc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro 465 470 475	1563
tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln 480 485 490	1611
ttt tcc tgg att atg cct gcc acc att aaa gaa aat atc atc ttt ggt Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly 495 500 505	1659
gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln 510 515 520 525	1707
cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu 530 535 540	1755
gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser 545 550 555	1803
tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser 560 565 570	1851
cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser 575 580 585	1899
tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser 590 595 600 605	1947
aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu 610 615 620	1995
ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln 625 630 635	2043
cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe 640 645 650	2091
agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe 655 660 665	2139
tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln 670 675 680 685	2187
tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile 690 695 700	2235

-continued

ctc aat cca atc aac tct gat atg gag agc ata cca gca gtg act aca Leu Asn Pro Ile Asn Ser Asp Met Glu Ser Ile Pro Ala Val Thr Thr	2283
705 710 715	
tgg aac aca tac ctt cga tat att act gtc cac aag agc tta att ttt Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe	2331
720 725 730	
gtg cta att tgg tgc tta gta att ttt ctg gca gag gtg gct gct tct Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser	2379
735 740 745	
ttg gtt gtg ctg tgg ctc ctt gga aac act cct ctt caa gac aaa ggg Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly	2427
750 755 760 765	
aat agt act cat agt aga aat aac agc tat gca gtg att atc acc agc Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser	2475
770 775 780	
acc agt tcg tat tat gtg ttt tac att tac gtg gga gta gcc gac act Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr	2523
785 790 795	
ttg ctt gct atg gga ttc ttc aga ggt cta cca ctg gtg cat act cta Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu	2571
800 805 810	
atc aca gtg tcg aaa att tta cac cac aaa atg tta cat tct gtt ctt Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu	2619
815 820 825	
caa gca cct atg tca acc ctc aac acg ttg aaa gca ggt ggg att ctt Gln Ala Pro Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu	2667
830 835 840 845	
aat aga ttc tcc aaa gat ata gca att ttg gat gac ctt ctg cct ctt Asn Arg Phe Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu	2715
850 855 860	
acc ata ttt gac ttc atc cag ttg tta tta att gtg att gga gct ata Thr Ile Phe Asp Phe Ile Gln Leu Leu Ile Val Ile Gly Ala Ile	2763
865 870 875	
gca gtt gtc gca gtt tta caa ccc tac atc ttt gtt gca aca gtg cca Ala Val Val Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro	2811
880 885 890	
gtg ata gtg gct ttt att atg ttg aga gca tat ttc ctc caa acc tca Val Ile Val Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser	2859
895 900 905	
cag caa ctc aaa caa ctg gaa tct gaa ggc agg agt cca att ttc act Gln Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr	2907
910 915 920 925	
cat ctt gtt aca agc tta aaa gga cta tgg aca ctt cgt gcc ttc gga His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly	2955
930 935 940	
cgg cag cct tac ttt gaa act ctg ttc cac aaa gct ctg aat tta cat Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His	3003
945 950 955	
act gcc aac tgg ttc ttg tac ctg tca aca ctg cgc tgg ttc caa atg Thr Ala Asn Trp Phe Leu Tyr 965 Thr Leu Arg Trp Phe Gln Met	3051
960 965 970	
aga ata gaa atg att ttt gtc atc ttc ttc att gct gtt acc ttc att Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile	3099
975 980 985	
tcc att tta aca aca gga gaa gga gaa gga aga gtt ggt att atc ctg Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu	3147
990 995 1000 1005	
act tta gcc atg aat atc atg agt aca ttg cag tgg gct gta aac tcc Thr Leu Ala Met Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser	3195
1010 1015 1020	

-continued

agc ata gat gtg gat agc ttg atg cga tct gtg agc cga gtc ttt aag	3243
Ser Ile Asp Val Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys	
1025 1030 1035	
ttc att gac atg cca aca gaa ggt aaa cct acc aag tca acc aaa cca	3291
Phe Ile Asp Met Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro	
1040 1045 1050	
tac aag aat ggc caa ctc tgc aaa gtt atg att att gag aat tca cac	3339
Tyr Lys Asn Gly Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His	
1055 1060 1065	
gtg aag aaa gat gac atc tgg ccc tca ggg ggc caa atg act gtc aaa	3387
Val Lys Lys Asp Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys	
1070 1075 1080 1085	
gat ctc aca gca aaa tac aca gaa ggt gga aat gcc ata tta gag aac	3435
Asp Leu Thr Ala Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn	
1090 1095 1100	
att tcc ttc tca ata agt cct ggc cag agg gtg ggc ctc ttg gga aga	3483
Ile Ser Phe Ser Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg	
1105 1110 1115	
act gga tca ggg aag agt act ttg tta tca gct ttt ttg aga cta ctg	3531
Thr Gly Ser Gly Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu	
1120 1125 1130	
aac act gaa gga gaa atc cag atc gat ggt gtg tct tgg gat tca ata	3579
Asn Thr Glu Gly Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile	
1135 1140 1145	
act ttg caa cag tgg agg aaa gcc ttt gga gtg ata cca cag aaa gta	3627
Thr Leu Gln Gln Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val	
1150 1155 1160 1165	
ttt att ttt tct gga aca ttt aga aaa aac ttg gat ccc tat gaa cag	3675
Phe Ile Phe Ser Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln	
1170 1175 1180	
tgg agt gat caa gaa ata tgg aaa gtt gca gat gag gtt ggg ctc aga	3723
Trp Ser Asp Gln Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg	
1185 1190 1195	
tct gtg ata gaa cag ttt cct ggg aag ctt gac ttt gtc ctt gtg gat	3771
Ser Val Ile Glu Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp	
1200 1205 1210	
ggg ggc tgt gtc cta agc cat ggc cac aag cag ttg atg tgc ttg gct	3819
Gly Gly Cys Val Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala	
1215 1220 1225	
aga tct gtt ctc agt aag gcg aag atc ttg ctg ctt gat gaa ccc agt	3867
Arg Ser Val Leu Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser	
1230 1235 1240 1245	
gct cat ttg gat cca gta aca tac caa ata att aga aga act cta aaa	3915
Ala His Leu Asp Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys	
1250 1255 1260	
caa gca ttt gct gat tgc aca gta att ctc tgt gaa cac agg ata gaa	3963
Gln Ala Phe Ala Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu	
1265 1270 1275	
gca atg ctg gaa tgc caa caa ttt ttg gtc ata gaa gag aac aaa gtg	4011
Ala Met Leu Glu Cys Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val	
1280 1285 1290	
cgg cag tac gat tcc atc cag aaa ctg ctg aac gag agg agc ctc ttc	4059
Arg Gln Tyr Asp Ser Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe	
1295 1300 1305	
cgg caa gcc atc agc ccc tcc gac agg gtg aag ctc ttt ccc cac cgg	4107
Arg Gln Ala Ile Ser Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg	
1310 1315 1320 1325	
aac tca agc aag tgc aag tct aag ccc cag att gct gct ctg aaa gag	4155
Asn Ser Ser Lys Cys Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu	

-continued

1330	1335	1340	
gag aca gaa gaa gag gtg caa gat aca agg ctt tag			4191
Glu Thr Glu Glu Glu Val Gln Asp Thr Arg Leu *			
1345	1350		
<p>&lt;210&gt; SEQ ID NO 2                      &lt;211&gt; LENGTH: 4419                      &lt;212&gt; TYPE: DNA                      &lt;213&gt; ORGANISM: homo sapiens                      &lt;220&gt; FEATURE:                      &lt;221&gt; NAME/KEY: CDS                      &lt;222&gt; LOCATION: (133)...(4419)</p>			
<p>&lt;400&gt; SEQUENCE: 2</p>			
aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca			60
gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccgagc			120
gcccagagaga cc atg cag agg tgg 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			

-continued

225			230			235			
gct ggg cta	ggg aga atg	atg atg atg	aag tac aga	gat cag aga	gct ggg		891		
Ala Gly Leu	Gly Arg Met	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 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 ttc	tca ggg ttc	ttt gtg		1083		
Val Arg Tyr	Phe Asn Ser	Ser Ala Phe	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 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 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 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		

-continued

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	ggt	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		
ggc	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	ggt	aac	caa	ggc	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	ggt	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		

-continued

tat gtg ttt tac att tac gtg gga gta gcc gac act ttg ctt gct atg Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met 865 870 875	2763
gga ttc ttc aga ggt cta cca ctg gtg cat act cta atc aca gtg tcg Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser 880 885 890	2811
aaa att tta cac cac aaa atg tta cat tct gtt ctt caa gca cct atg Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro Met 895 900 905	2859
tca acc ctc aac acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser 910 915 920 925	2907
aaa gat ata gca att ttg gat gac ctt ctg cct ctt acc ata ttt gac Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp 930 935 940	2955
ttc atc cag ttg tta tta att gtg att gga gct ata gca gtt gtc gca Phe Ile Gln Leu Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala 945 950 955	3003
gtt tta caa ccc tac atc ttt gtt gca aca gtg cca gtg ata gtg gct Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala 960 965 970	3051
ttt att atg ttg aga gca tat ttc ctc caa acc tca cag caa ctc aaa Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys 975 980 985	3099
caa ctg gaa tct gaa ggc agg agt cca att ttc act cat ctt gtt aca Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr 990 995 1000 1005	3147
agc tta aaa gga cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr 1010 1015 1020	3195
ttt gaa act ctg ttc cac aaa gct ctg aat tta cat act gcc aac tgg Phe Glu Thr Leu Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp 1025 1030 1035	3243
ttc ttg tac ctg tca aca ctg cgc tgg ttc caa atg aga ata gaa atg Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met 1040 1045 1050	3291
att ttt gtc atc ttc ttc att gct gtt acc ttc att tcc att tta aca Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr 1055 1060 1065	3339
aca gga gaa gga gaa gga aga gtt ggt att atc ctg act tta gcc atg Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met 1070 1075 1080 1085	3387
aat atc atg agt aca ttg cag tgg gct gta aac tcc agc ata gat gtg Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val 1090 1095 1100	3435
gat agc ttg atg cga tct gtg agc cga gtc ttt aag ttc att gac atg Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met 1105 1110 1115	3483
cca aca gaa ggt aaa cct acc aag tca acc aaa cca tac aag aat ggc Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly 1120 1125 1130	3531
caa ctc tcg aaa gtt atg att att gag aat tca cac gtg aag aaa gat Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp 1135 1140 1145	3579
gac atc tgg ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala 1150 1155 1160 1165	3627
aaa tac aca gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca Lys Tyr Thr Glu Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser 1170 1175 1180	3675



-continued

---

```

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 gcc 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

```

```

<210> SEQ ID NO 3
<211> LENGTH: 4410
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (133)...(4410)

```

<400> SEQUENCE: 3

```

aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca 60
gagtagtagg tctttggcat taggagcttg agcccagacg gcctagcag ggaccccagc 120

```

-continued

---

gcccagagaga 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 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	

-continued

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

-continued

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	ggt	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		

-continued

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	

-continued

---

```

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

<210> SEQ ID NO 4
<211> LENGTH: 4371
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (133)...(4371)

<400> SEQUENCE: 4
aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca    60
gagtagtagg tctttggcat taggagcttg agcccagacg gcctagcag ggaccccagc    120
gcccagagaga cc atg cag agg tgg 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

```

-continued

ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val 80 85 90	411
acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr 95 100 105	459
gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile 110 115 120 125	507
ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc Gly Leu Cys Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala 130 135 140	555
att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe 145 150 155	603
agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp 160 165 170	651
aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn 175 180 185	699
aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro 190 195 200 205	747
ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala 210 215 220	795
tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln 225 230 235	843
gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly 240 245 250	891
aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile 255 260 265	939
caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile 270 275 280 285	987
gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr 290 295 300	1035
gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val 305 310 315	1083
gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu 320 325 330	1131
cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala 335 340 345	1179
gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu 350 355 360 365	1227
gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys 370 375 380	1275
aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val 1323	1323

-continued

385			390			395								
aca gcc ttc	tg	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	ggt	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 gcc 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					
ggt 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	ggt	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	ggt	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



-continued

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	ggc	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	ggt	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	ggc	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	ggt	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	ggt	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	ggt	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			

-continued

ttc ttg tac ctg tca aca ctg cgc tgg ttc caa atg aga ata gaa atg Phe Leu Tyr Leu Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met 1025 1030 1035	3243
att ttt gtc atc ttc ttc att gct gtt acc ttc att tcc att tta aca Ile Phe Val Ile Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr 1040 1045 1050	3291
aca gga gaa gga gaa gga aga gtt ggt att atc ctg act tta gcc atg Thr Gly Glu Gly Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met 1055 1060 1065	3339
aat atc atg agt aca ttg cag tgg gct gta aac tcc agc ata gat gtg Asn Ile Met Ser Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val 1070 1075 1080 1085	3387
gat agc ttg atg cga tct gtg agc cga gtc ttt aag ttc att gac atg Asp Ser Leu Met Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met 1090 1095 1100	3435
cca aca gaa ggt aaa cct acc aag tca acc aaa cca tac aag aat ggc Pro Thr Glu Gly Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly 1105 1110 1115	3483
caa ctc tcg aaa gtt atg att att gag aat tca cac gtg aag aaa gat Gln Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp 1120 1125 1130	3531
gac atc tgg ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca Asp Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala 1135 1140 1145	3579
aaa tac aca gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca Lys Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser 1150 1155 1160 1165	3627
ata agt cct ggc cag agg gtg ggc ctc ttg gga aga act gga tca ggg Ile Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly 1170 1175 1180	3675
aag agt act ttg tta tca gct ttt ttg aga cta ctg aac act gaa gga Lys Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly 1185 1190 1195	3723
gaa atc cag atc gat ggt gtg tct tgg gat tca ata act ttg caa cag Glu Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln 1200 1205 1210	3771
tgg agg aaa gcc ttt gga gtg ata cca cag aaa gta ttt att ttt tct Trp Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser 1215 1220 1225	3819
gga aca ttt aga aaa aac ttg gat ccc tat gaa cag tgg agt gat caa Gly Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln 1230 1235 1240 1245	3867
gaa ata tgg aaa gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa Glu Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu 1250 1255 1260	3915
cag ttt cct ggg aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc Gln Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val 1265 1270 1275	3963
cta agc cat ggc cac aag cag ttg atg tgc ttg gct aga tct gtt ctc Leu Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu 1280 1285 1290	4011
agt aag gcg aag atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat Ser Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp 1295 1300 1305	4059
cca gta aca tac caa ata att aga aga act cta aaa caa gca ttt gct Pro Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala 1310 1315 1320 1325	4107
gat tgc aca gta att ctc tgt gaa cac agg ata gaa gca atg ctg gaa Asp Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu 1330 1335 1340	4155

-continued

---

```

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 Thr Glu Glu
1390                      1395                      1400                      1405

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

<210> SEQ ID NO 5
<211> LENGTH: 4368
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (133)...(4368)

<400> SEQUENCE: 5

aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca      60
gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccgag      120
gcccagagaga cc atg cag agg tgg 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

```

-continued

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn 175 180 185	699
aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro 190 195 200 205	747
ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala 210 215 220	795
tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln 225 230 235	843
gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly 240 245 250	891
aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile 255 260 265	939
caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile 270 275 280 285	987
gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr 290 295 300	1035
gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val 305 310 315	1083
gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu 320 325 330	1131
cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala 335 340 345	1179
gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu 350 355 360 365	1227
gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys 370 375 380	1275
aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val 385 390 395	1323
aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys 400 405 410	1371
caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe 415 420 425	1419
ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn 430 435 440 445	1467
ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly 450 455 460	1515
gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro 465 470 475	1563
tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln	1611

-continued

480	485	490	
ttt tcc tgg att atg Phe Ser Trp Ile Met 495	cct ggc acc att Pro Gly Thr Ile 500	aaa gaa aat atc atc Lys Glu Asn Ile Ile 505	ttt ggt Phe Gly 1659
gtt tcc tat gat gaa Val Ser Tyr Asp Glu 510	tat aga tac aga Tyr Arg Tyr Arg 515	agc gtc atc aaa Ser Val Ile Lys 520	gca tgc caa Ala Cys Gln 525
cta gaa gag gac atc Leu Glu Glu Asp Ile 530	tcc aag ttt gca Ser Lys Phe Ala 535	gag aaa gac aat Glu Lys Asp Asn 540	ata gtt ctt Ile Val Leu 540
gga gaa ggt gga atc Gly Glu Gly Gly Ile 545	aca ctg agt gga Thr Leu Ser Gly 550	ggt caa cga gca Gly Gln Arg Ala 555	aga att tct Arg Ile Ser 555
tta gca aga gca gta Leu Ala Arg Ala Val 560	tac aaa gat gct Tyr Lys Asp Ala 565	gat gat ttg tat tta Ala Asp Leu Tyr Leu 570	tta gac tct Leu Leu Asp Ser 570
cct ttt gga tac cta Pro Phe Gly Tyr Leu 575	gat gtt tta aca Val Leu Thr Glu 580	gaa aaa gaa ata Lys Glu Lys Ile Phe 585	ttt gaa agc Phe Glu Ser 585
tgt gtc tgt aaa ctg Cys Val Cys Lys Leu 590	atg gct aac aaa Met Ala Asn Lys 595	act agg att ttg Thr Arg Ile Leu 600	gtc act tct Val Thr Ser 605
aaa atg gaa cat tta Lys Met Glu His Leu 610	aag aaa gct gac Lys Lys Ala Asp 615	ata tta att ttg Ile Leu Ile Leu 620	cat gaa His Glu 620
ggt agc agc tat ttt Gly Ser Ser Tyr Phe 625	tat ggg aca ttt Tyr Gly Thr Phe 630	tca gaa ctc caa Glu Leu Gln Asn 635	aat cta cag Leu Gln 635
cca gac ttt agc tca Pro Asp Phe Ser Ser 640	aaa ctc atg gga Lys Leu Met Gly 645	tgt gat tct ttc Cys Asp Ser Phe 650	gac caa ttt Asp Gln Phe 650
agt gca gaa aga aga Ser Ala Glu Arg Arg 655	aat tca atc cta Asn Ser Ile Leu 660	act gag acc tta Thr Glu Thr Leu 665	cac cgt ttc His Arg Phe 665
tca tta gaa gga gat Ser Leu Glu Gly Asp 670	gct cct gtc tcc Ala Pro Val Ser 675	tgg aca gaa aca Thr Trp Thr Glu 680	aaa aaa caa Lys Lys Gln 685
tct ttt aaa cag act Ser Phe Lys Gln Thr 690	gga gag ttt ggg Gly Glu Phe Gly 695	gaa aaa agg aag Glu Lys Arg Lys 700	aat tct att Asn Ser Ile 700
ctc aat cca atc aac Leu Asn Pro Ile Asn 705	tct acg ctt cag Ser Thr Leu Gln 710	gca cga agg agg Ala Arg Arg Arg 715	cag tct gtc Gln Ser Val 715
ctg aac ctg atg aca Leu Asn Leu Met Thr 720	cac tca gtt aac His Ser Val Asn 725	caa ggt cag aac Gln Gly Gln Asn 730	att cac cga Ile His Arg 730
aag aca aca gca tcc Lys Thr Thr Ala Ser 735	aca cga aaa gtg Thr Arg Lys Val 740	tca ctg gcc cct Ser Leu Ala Pro 745	cag gca aac Gln Ala Asn 745
ttg act gaa ctg gat Leu Thr Glu Leu Asp 750	ata tat tca aga Ile Tyr Ser Arg 755	agg tta tct caa Arg Arg Leu Ser 760	gaa act ggc Gln Glu Thr Gly 765
ttg gat atg gag agc Leu Asp Met Glu Ser 770	ata cca gca gtg Ile Pro Ala Val 775	act aca tgg aac Thr Thr Trp Asn 780	aca tac ctt Thr Tyr Leu 780
cga tat att act gtc Arg Tyr Ile Thr Val 785	cac aag agc tta His Lys Ser Leu 790	att ttt gtg cta Ile Phe Val Leu 795	att tgg tgc Ile Trp Cys 795
tta gta att ttt ctg Leu Thr Ile Thr Val 800	gca gag gtg gct Gly Arg Thr Val 805	gct gct tct ttg Gly Thr Val Leu 810	gtg ctg tgg Thr Cys Gln 810

-continued

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 Ile Val Ile Gly Ala Ile Val 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	

-continued

ctc tcg aaa gtt atg att att gag aat tca cac gtg aag aaa gat gac Leu Ser Lys Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp 1120 1125 1130	3531
atc tgg ccc tca ggg ggc caa atg act gtc aaa gat ctc aca gca aaa Ile Trp Pro Ser Gly Gly Gln Met Thr Val Lys Asp Leu Thr Ala Lys 1135 1140 1145	3579
tac aca gaa ggt gga aat gcc ata tta gag aac att tcc ttc tca ata Tyr Thr Glu Gly Gly Asn Ala Ile Leu Glu Asn Ile Ser Phe Ser Ile 1150 1155 1160 1165	3627
agt cct ggc cag agg gtg ggc ctc ttg gga aga act gga tca ggg aag Ser Pro Gly Gln Arg Val Gly Leu Leu Gly Arg Thr Gly Ser Gly Lys 1170 1175 1180	3675
agt act ttg tta tca gct ttt ttg aga cta ctg aac act gaa gga gaa Ser Thr Leu Leu Ser Ala Phe Leu Arg Leu Leu Asn Thr Glu Gly Glu 1185 1190 1195	3723
atc cag atc gat ggt gtg tct tgg gat tca ata act ttg caa cag tgg Ile Gln Ile Asp Gly Val Ser Trp Asp Ser Ile Thr Leu Gln Gln Trp 1200 1205 1210	3771
agg aaa gcc ttt gga gtg ata cca cag aaa gta ttt att ttt tct gga Arg Lys Ala Phe Gly Val Ile Pro Gln Lys Val Phe Ile Phe Ser Gly 1215 1220 1225	3819
aca ttt aga aaa aac ttg gat ccc tat gaa cag tgg agt gat caa gaa Thr Phe Arg Lys Asn Leu Asp Pro Tyr Glu Gln Trp Ser Asp Gln Glu 1230 1235 1240 1245	3867
ata tgg aaa gtt gca gat gag gtt ggg ctc aga tct gtg ata gaa cag Ile Trp Lys Val Ala Asp Glu Val Gly Leu Arg Ser Val Ile Glu Gln 1250 1255 1260	3915
ttt cct ggg aag ctt gac ttt gtc ctt gtg gat ggg ggc tgt gtc cta Phe Pro Gly Lys Leu Asp Phe Val Leu Val Asp Gly Gly Cys Val Leu 1265 1270 1275	3963
agc cat ggc cac aag cag ttg atg tgc ttg gct aga tct gtt ctc agt Ser His Gly His Lys Gln Leu Met Cys Leu Ala Arg Ser Val Leu Ser 1280 1285 1290	4011
aag gcg aag atc ttg ctg ctt gat gaa ccc agt gct cat ttg gat cca Lys Ala Lys Ile Leu Leu Leu Asp Glu Pro Ser Ala His Leu Asp Pro 1295 1300 1305	4059
gta aca tac caa ata att aga aga act cta aaa caa gca ttt gct gat Val Thr Tyr Gln Ile Ile Arg Arg Thr Leu Lys Gln Ala Phe Ala Asp 1310 1315 1320 1325	4107
tgc aca gta att ctc tgt gaa cac agg ata gaa gca atg ctg gaa tgc Cys Thr Val Ile Leu Cys Glu His Arg Ile Glu Ala Met Leu Glu Cys 1330 1335 1340	4155
caa caa ttt ttg gtc ata gaa gag aac aaa gtg cgg cag tac gat tcc Gln Gln Phe Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser 1345 1350 1355	4203
atc cag aaa ctg ctg aac gag agg agc ctc ttc cgg caa gcc atc agc Ile Gln Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser 1360 1365 1370	4251
ccc tcc gac agg gtg aag ctc ttt ccc cac cgg aac tca agc aag tgc Pro Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys 1375 1380 1385	4299
aag tct aag ccc cag att gct gct ctg aaa gag gag aca gaa gaa gag Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu Glu 1390 1395 1400 1405	4347
gtg caa gat aca agg ctt tag Val Gln Asp Thr Arg Leu * 1410	4368

-continued

```

<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (133)...(4347)

<400> SEQUENCE: 6

aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca      60
gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccagc      120
gcccagagaga cc atg cag agg tgg 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

```



-continued

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	

-continued

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	
ggc 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 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 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 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	Asp Ser	Asp Ser	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 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 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	ggc 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 Thr	Ile Thr	Val Ser	Lys Ile	Leu His	His Lys Met Leu	
		865		870		875	
cat tct	ggt 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	
ggc ggg	att ctt	aat aga	ttc tcc	aaa gat	ata gca	att ttg gat gac	2859

-continued

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	ggt	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			



-continued

gct tca aag aaa aat cct aaa ctc att aat gcc ctt cgg cga tgt ttt Ala Ser Lys Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe 65 70 75	363
ttc tgg aga ttt atg ttc tat gga atc ttt tta tat tta ggg gaa gtc Phe Trp Arg Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val 80 85 90	411
acc aaa gca gta cag cct ctc tta ctg gga aga atc ata gct tcc tat Thr Lys Ala Val Gln Pro Leu Leu Leu Gly Arg Ile Ile Ala Ser Tyr 95 100 105	459
gac ccg gat aac aag gag gaa cgc tct atc gcg att tat cta ggc ata Asp Pro Asp Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile 110 115 120 125	507
ggc tta tgc ctt ctc ttt att gtg agg aca ctg ctc cta cac cca gcc Gly Leu Cys Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala 130 135 140	555
att ttt ggc ctt cat cac att gga atg cag atg aga ata gct atg ttt Ile Phe Gly Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe 145 150 155	603
agt ttg att tat aag aag act tta aag ctg tca agc cgt gtt cta gat Ser Leu Ile Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp 160 165 170	651
aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn 175 180 185	699
aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro 190 195 200 205	747
ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala 210 215 220	795
tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln 225 230 235	843
gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly 240 245 250	891
aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile 255 260 265	939
caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile 270 275 280 285	987
gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr 290 295 300	1035
gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val 305 310 315	1083
gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu 320 325 330	1131
cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala 335 340 345	1179
gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu 350 355 360 365	1227
gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys 370 375 380	1275

-continued

aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val 385 390 395	1323
aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys 400 405 410	1371
caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe 415 420 425	1419
ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn 430 435 440 445	1467
ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly 450 455 460	1515
gca gcc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro 465 470 475	1563
tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln 480 485 490	1611
ttt tcc tgg att atg cct gcc acc att aaa gaa aat atc atc ttt ggt Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly 495 500 505	1659
gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln 510 515 520 525	1707
cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu 530 535 540	1755
gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct Gly Glu Gly Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser 545 550 555	1803
tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser 560 565 570	1851
cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser 575 580 585	1899
tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser 590 595 600 605	1947
aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu 610 615 620	1995
ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln 625 630 635	2043
cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe 640 645 650	2091
agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe 655 660 665	2139
tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln 670 675 680 685	2187
tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile	2235



-continued

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 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	



-continued

---

```

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 8
<211> LENGTH: 4311
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (133)...(4311)

<400> SEQUENCE: 8

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

```

-continued

aaa ata agt att gga caa ctt gtt agt ctc ctt tcc aac aac ctg aac Lys Ile Ser Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn 175 180 185	699
aaa ttt gat gaa gga ctt gca ttg gca cat ttc gtg tgg atc gct cct Lys Phe Asp Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro 190 195 200 205	747
ttg caa gtg gca ctc ctc atg ggg cta atc tgg gag ttg tta cag gcg Leu Gln Val Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala 210 215 220	795
tct gcc ttc tgt gga ctt ggt ttc ctg ata gtc ctt gcc ctt ttt cag Ser Ala Phe Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln 225 230 235	843
gct ggg cta ggg aga atg atg atg aag tac aga gat cag aga gct ggg Ala Gly Leu Gly Arg Met Met Met Lys Tyr Arg Asp Gln Arg Ala Gly 240 245 250	891
aag atc agt gaa aga ctt gtg att acc tca gaa atg att gaa aat atc Lys Ile Ser Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile 255 260 265	939
caa tct gtt aag gca tac tgc tgg gaa gaa gca atg gaa aaa atg att Gln Ser Val Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile 270 275 280 285	987
gaa aac tta aga caa aca gaa ctg aaa ctg act cgg aag gca gcc tat Glu Asn Leu Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr 290 295 300	1035
gtg aga tac ttc aat agc tca gcc ttc ttc ttc tca ggg ttc ttt gtg Val Arg Tyr Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val 305 310 315	1083
gtg ttt tta tct gtg ctt ccc tat gca cta atc aaa gga atc atc ctc Val Phe Leu Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu 320 325 330	1131
cgg aaa ata ttc acc acc atc tca ttc tgc att gtt ctg cgc atg gcg Arg Lys Ile Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala 335 340 345	1179
gtc act cgg caa ttt ccc tgg gct gta caa aca tgg tat gac tct ctt Val Thr Arg Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu 350 355 360 365	1227
gga gca ata aac aaa ata cag gat ttc tta caa aag caa gaa tat aag Gly Ala Ile Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys 370 375 380	1275
aca ttg gaa tat aac tta acg act aca gaa gta gtg atg gag aat gta Thr Leu Glu Tyr Asn Leu Thr Thr Thr Glu Val Val Met Glu Asn Val 385 390 395	1323
aca gcc ttc tgg gag gag gga ttt ggg gaa tta ttt gag aaa gca aaa Thr Ala Phe Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys 400 405 410	1371
caa aac aat aac aat aga aaa act tct aat ggt gat gac agc ctc ttc Gln Asn Asn Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe 415 420 425	1419
ttc agt aat ttc tca ctt ctt ggt act cct gtc ctg aaa gat att aat Phe Ser Asn Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn 430 435 440 445	1467
ttc aag ata gaa aga gga cag ttg ttg gcg gtt gct gga tcc act gga Phe Lys Ile Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly 450 455 460	1515
gca ggc aag act tca ctt cta atg atg att atg gga gaa ctg gag cct Ala Gly Lys Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro 465 470 475	1563
tca gag ggt aaa att aag cac agt gga aga att tca ttc tgt tct cag Ser Glu Gly Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln 480 485 490	1611

-continued

ttt tcc tgg att atg cct ggc acc att aaa gaa aat atc atc ttt ggt Phe Ser Trp Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly 495 500 505	1659
gtt tcc tat gat gaa tat aga tac aga agc gtc atc aaa gca tgc caa Val Ser Tyr Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln 510 515 520 525	1707
cta gaa gag gac atc tcc aag ttt gca gag aaa gac aat ata gtt ctt Leu Glu Glu Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu 530 535 540	1755
gga gaa ggt gga atc aca ctg agt gga ggt caa cga gca aga att tct Gly Glu Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser 545 550 555	1803
tta gca aga gca gta tac aaa gat gct gat ttg tat tta tta gac tct Leu Ala Arg Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser 560 565 570	1851
cct ttt gga tac cta gat gtt tta aca gaa aaa gaa ata ttt gaa agc Pro Phe Gly Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser 575 580 585	1899
tgt gtc tgt aaa ctg atg gct aac aaa act agg att ttg gtc act tct Cys Val Cys Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser 590 595 600 605	1947
aaa atg gaa cat tta aag aaa gct gac aaa ata tta att ttg cat gaa Lys Met Glu His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu His Glu 610 615 620	1995
ggt agc agc tat ttt tat ggg aca ttt tca gaa ctc caa aat cta cag Gly Ser Ser Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln 625 630 635	2043
cca gac ttt agc tca aaa ctc atg gga tgt gat tct ttc gac caa ttt Pro Asp Phe Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe 640 645 650	2091
agt gca gaa aga aga aat tca atc cta act gag acc tta cac cgt ttc Ser Ala Glu Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe 655 660 665	2139
tca tta gaa gga gat gct cct gtc tcc tgg aca gaa aca aaa aaa caa Ser Leu Glu Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln 670 675 680 685	2187
tct ttt aaa cag act gga gag ttt ggg gaa aaa agg aag aat tct att Ser Phe Lys Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile 690 695 700	2235
ctc aat cca atc aac tct cac cga aag aca aca gca tcc aca cga aaa Leu Asn Pro Ile Asn Ser His Arg Lys Thr Thr Ala Ser Thr Arg Lys 705 710 715	2283
gtg tca ctg gcc cct cag gca aac ttg act gaa ctg gat ata tat tca Val Ser Leu Ala Pro Gln Ala Asn Leu Thr Glu Leu Asp Ile Tyr Ser 720 725 730	2331
aga agg tta tct caa gaa act ggc ttg gaa ata agt gaa gaa gat atg Arg Arg Leu Ser Gln Glu Thr Gly Leu Glu Ile Ser Glu Glu Asp Met 735 740 745	2379
gag agc ata cca gca gtg act aca tgg aac aca tac ctt cga tat att Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile 750 755 760 765	2427
act gtc cac aag agc tta att ttt gtg cta att tgg tgc tta gta att Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile 770 775 780	2475
ttt ctg gca gag gtg gct gct tct ttg gtt gtg ctg tgg ctc ctt gga Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly 785 790 795	2523
aac act cct ctt caa gac aaa ggg aat agt act cat agt aga aat aac Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn	2571

-continued

800	805	810	
agc tat gca gtg att atc acc agc acc agt tcg tat tat gtg ttt tac Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr 815 820 825			2619
att tac gtg gga gta gcc gac act ttg ctt gct atg gga ttc ttc aga Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg 830 835 840 845			2667
ggc cta cca ctg gtg cat act cta atc aca gtg tcg aaa att tta cac Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His 850 855 860			2715
cac aaa atg tta cat tct gtt ctt caa gca cct atg tca acc ctc aac His Lys Met Leu His Ser Val Leu Gln Ala Pro Met Ser Thr Leu Asn 865 870 875			2763
acg ttg aaa gca ggt ggg att ctt aat aga ttc tcc aaa gat ata gca Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe Ser Lys Asp Ile Ala 880 885 890			2811
att ttg gat gac ctt ctg cct ctt acc ata ttt gac ttc atc cag ttg Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe Asp Phe Ile Gln Leu 895 900 905			2859
tta tta att gtg att gga gct ata gca gtt gtc gca gtt tta caa ccc Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val Ala Val Leu Gln Pro 910 915 920 925			2907
tac atc ttt gtt gca aca gtg cca gtg ata gtg gct ttt att atg ttg Tyr Ile Phe Val Ala Thr Val Pro Val Ile Val Ala Phe Ile Met Leu 930 935 940			2955
aga gca tat ttc ctc caa acc tca cag caa ctc aaa caa ctg gaa tct Arg Ala Tyr Phe Leu Gln Thr Ser Gln Gln Leu Lys Gln Leu Glu Ser 945 950 955			3003
gaa ggc agg agt cca att ttc act cat ctt gtt aca agc tta aaa gga Glu Gly Arg Ser Pro Ile Phe Thr His Leu Val Thr Ser Leu Lys Gly 960 965 970			3051
cta tgg aca ctt cgt gcc ttc gga cgg cag cct tac ttt gaa act ctg Leu Trp Thr Leu Arg Ala Phe Gly Arg Gln Pro Tyr Phe Glu Thr Leu 975 980 985			3099
ttc cac aaa gct ctg aat tta cat act gcc aac tgg ttc ttg tac ctg Phe His Lys Ala Leu Asn Leu His Thr Ala Asn Trp Phe Leu Tyr Leu 990 995 1000 1005			3147
tca aca ctg cgc tgg ttc caa atg aga ata gaa atg att ttt gtc atc Ser Thr Leu Arg Trp Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile 1010 1015 1020			3195
ttc ttc att gct gtt acc ttc att tcc att tta aca aca gga gaa gga Phe Phe Ile Ala Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly 1025 1030 1035			3243
gaa gga aga gtt ggt att atc ctg act tta gcc atg aat atc atg agt Glu Gly Arg Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser 1040 1045 1050			3291
aca ttg cag tgg gct gta aac tcc agc ata gat gtg gat agc ttg atg Thr Leu Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met 1055 1060 1065			3339
cga tct gtg agc cga gtc ttt aag ttc att gac atg cca aca gaa ggt Arg Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly 1070 1075 1080 1085			3387
aaa cct acc aag tca acc aaa cca tac aag aat ggc caa ctc tcg aaa Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Ser Gly Gln Leu Ser Lys 1090 1095 1100			3435
ggt atg att att gag aat tca cac gtg aag aaa gat gac atc tgg ccc Val Met Ile Ile Glu Asn Ser His Val Lys Lys Asp Asp Ile Trp Pro 1105 1110 1115			3483
tca ggg ggc caa atg act gtc aaa gat ctc aca gca aaa tac aca gaa			3531

-continued

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	
ggt 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

-continued

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				

-continued

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	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			

-continued

---

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



-continued

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

-continued

---

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

-continued

---

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				



-continued

---

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

-continued

---

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	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		

-continued

---

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

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

-continued

---

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



-continued

---

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

-continued

---

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

-continued

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 Leu Asn Thr	Glu Gly Glu Ile Gln
	1185	1190	1195
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
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
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

-continued

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				

-continued

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	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	

-continued

---

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

-continued

---

```

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

```

-continued

---

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



-continued

---

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

-continued

---

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

-continued

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

-continued

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

-continued

---

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

-continued

---

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

-continued

---

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

-continued

---

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



-continued

---

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.

\* \* \* \* \*