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(54) **NUCLEIC ACID ENCODING SODIUM CHANNEL SUBUNIT**

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C12N 15/12 (2006.01)
C12N 5/10 (2006.01)
C12N 15/63 (2006.01)

(52) **U.S. Cl.** **435/320.1**; 435/325; 536/23.1; 536/23.5; 536/24.1

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

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GenBank Accession No. AY038064 (available starting Aug. 1, 2001).
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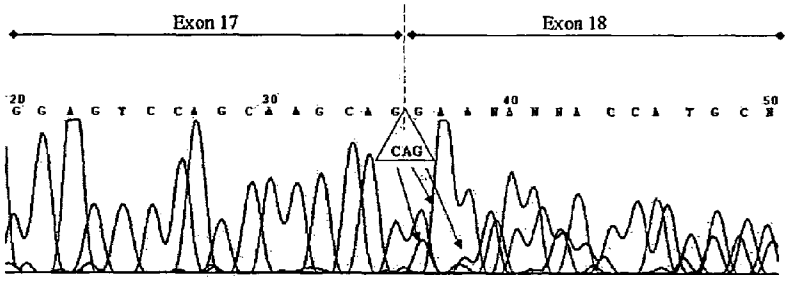
(57) **ABSTRACT**

The present invention discloses four groups of SCN5A variants that represent the most common SCN5A variants in humans. A specific mutation in one of the variants has been shown to display a different phenotype in relation to a human heart disease than other variants and known human sodium channel α subunits with corresponding mutations. The present invention provides new tools to study mutations and to design or identify new diagnostic and treatment strategies or agents for sodium channel related diseases or conditions.

6 Claims, 6 Drawing Sheets



SEQ ID NO:18

mRNA (Alternative Splicing)

Exon 17 Exon 18

TGG GCA CGG AGG GAG TCC AGC AAG CAG GAA TCC CAG CCT GTG TCC SEQ ID NO:19

K Q E S
1075 1076 1077 1078

TGG GCA CGG AGG GAG TCC AGC AAG CAG CAG GAA TCC CAG CCT GTG TCC SEQ ID NO:20

K Q Q E S
1075 1076 1077 1078 1079

Genomic DNA

GAG TCC AGC AAG CAG gtg ggc cct.....ggg tct ttt cag cag GAA TCC CAG CCT GTG TCC SEQ ID NO:21

Exon 17 Splice Donor Splice Acceptor Exon 18

FIG. 1

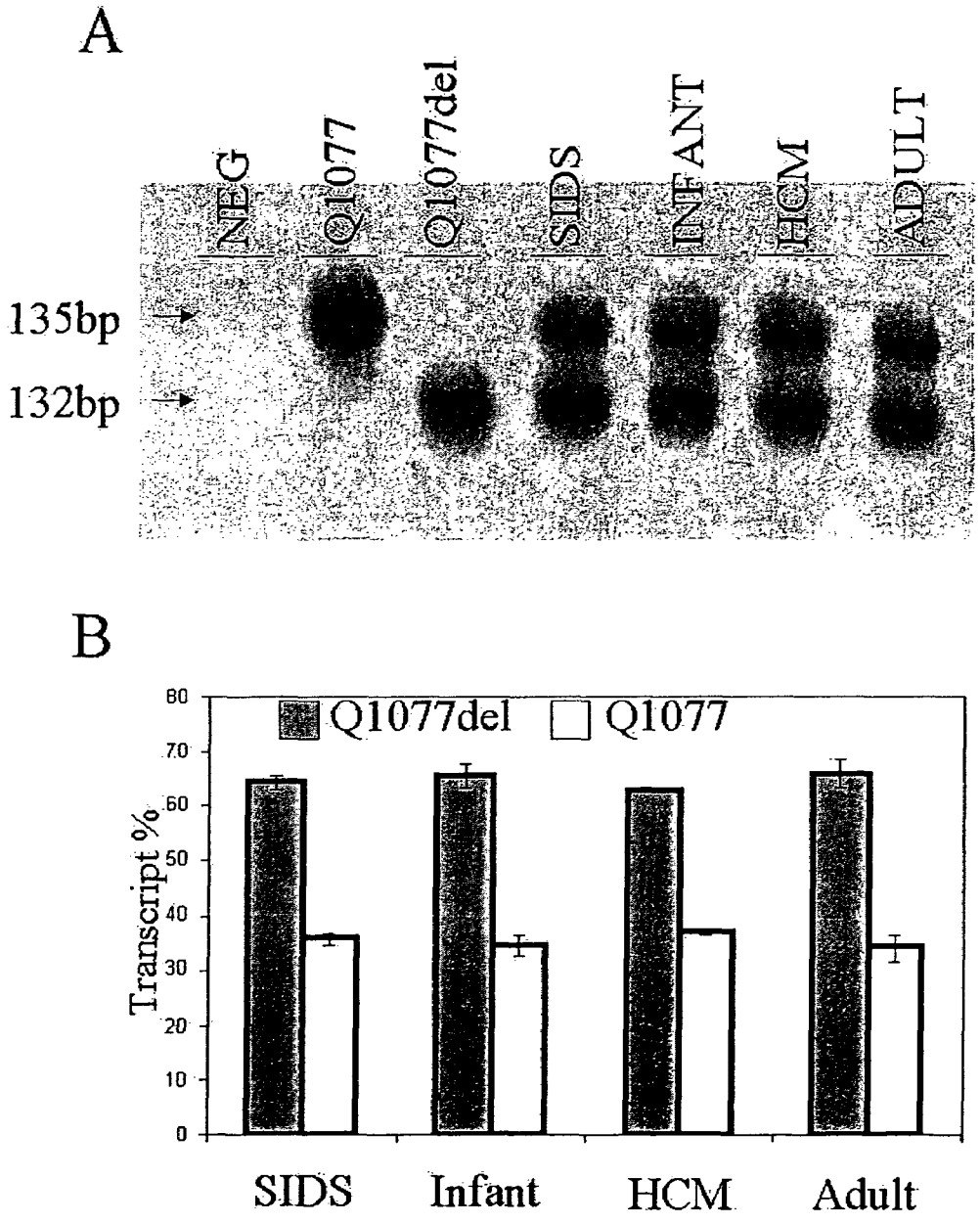

A
NEG
Q1077
Q1077del
SIDS
INFANT
HCM
ADULT
135bp
132bp
B
Q1077del
Q1077
Transcript %
0
10
20
30
40
50
60
70
80
SIDS
Infant
HCM
Adult

FIG. 2

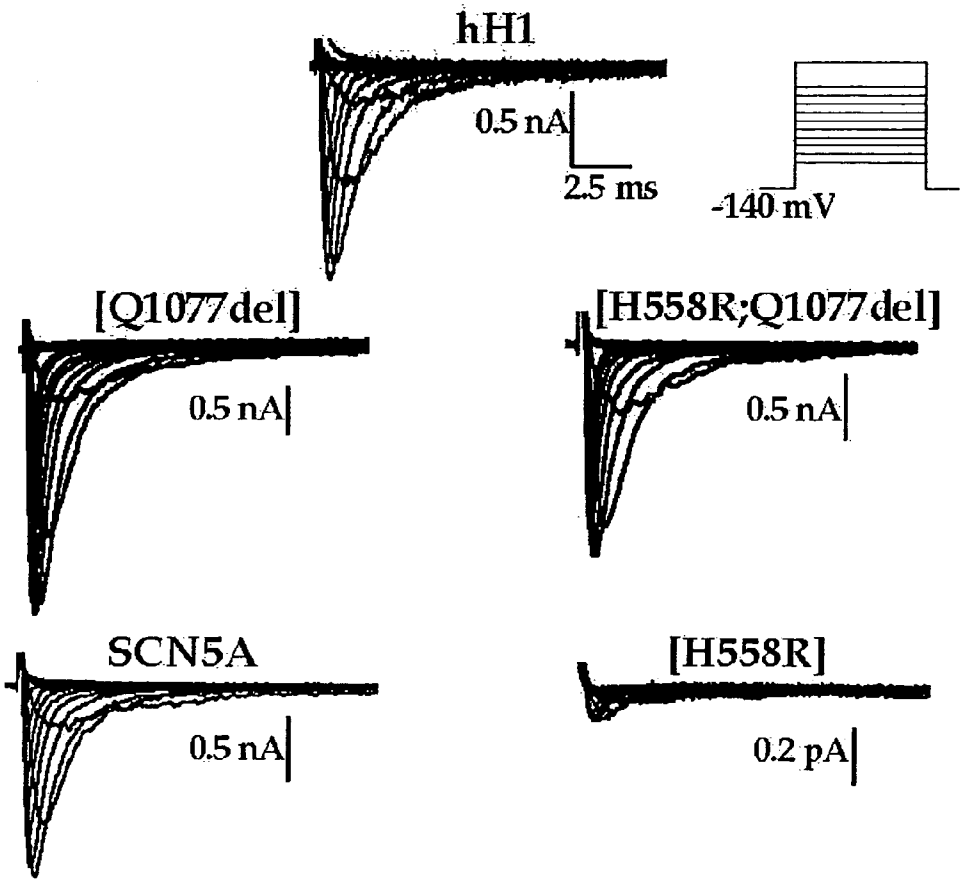

hH1
0.5 nA
2.5 ms
-140 mV
[Q1077del]
0.5 nA
[H558R;Q1077del]
0.5 nA
SCN5A
0.5 nA
[H558R]
0.2 pA

FIG. 3

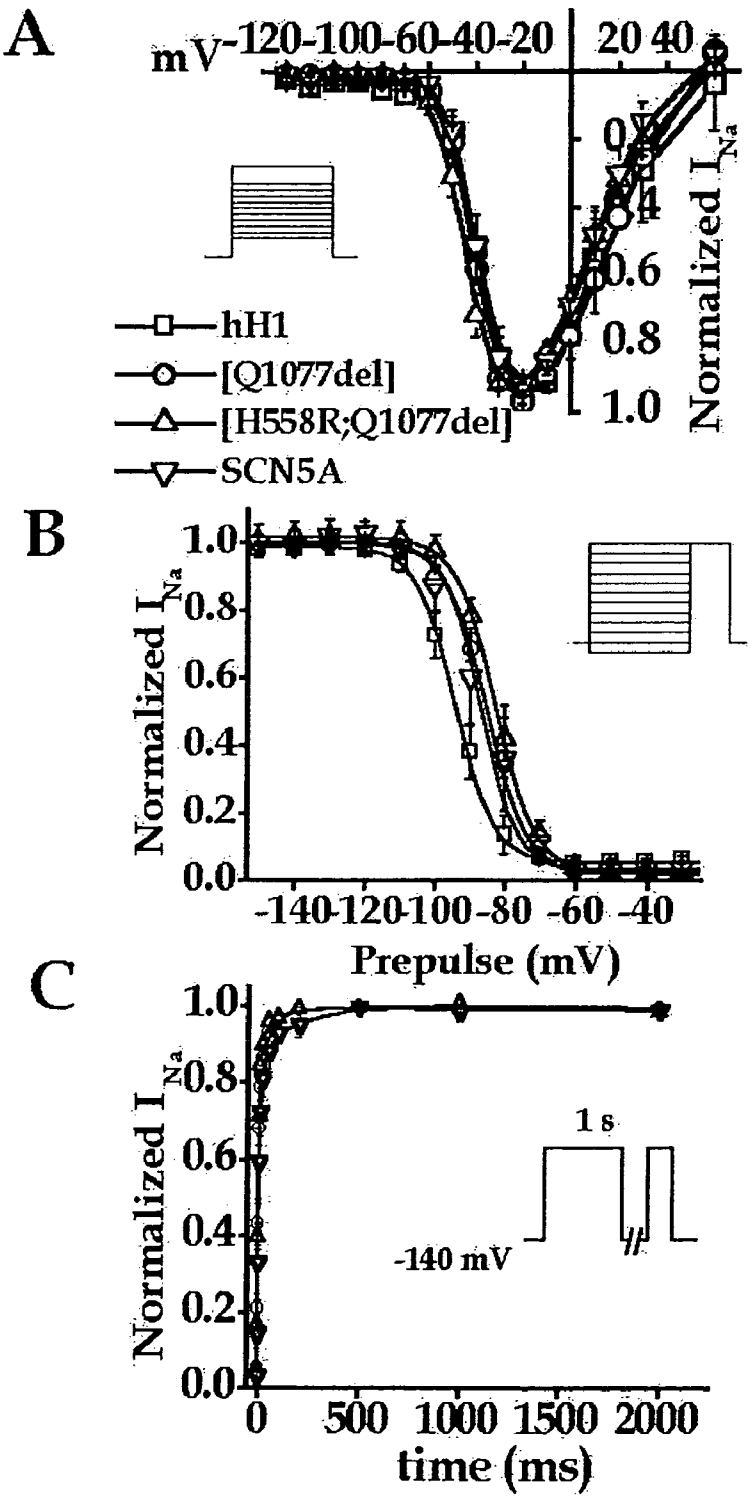

A
mV -120 -100 -60 -40 -20 20 40
0.4
0.6
0.8
1.0
Normalized I_{Na}
hH1
[Q1077del]
[H558R;Q1077del]
SCN5A
B
1.0
0.8
0.6
0.4
0.2
0.0
Normalized I_{Na}
-140 -120 -100 -80 -60 -40
Prepulse (mV)
C
1.0
0.8
0.6
0.4
0.2
0.0
Normalized I_{Na}
1 s
-140 mV
0 500 1000 1500 2000
time (ms)

FIG. 4

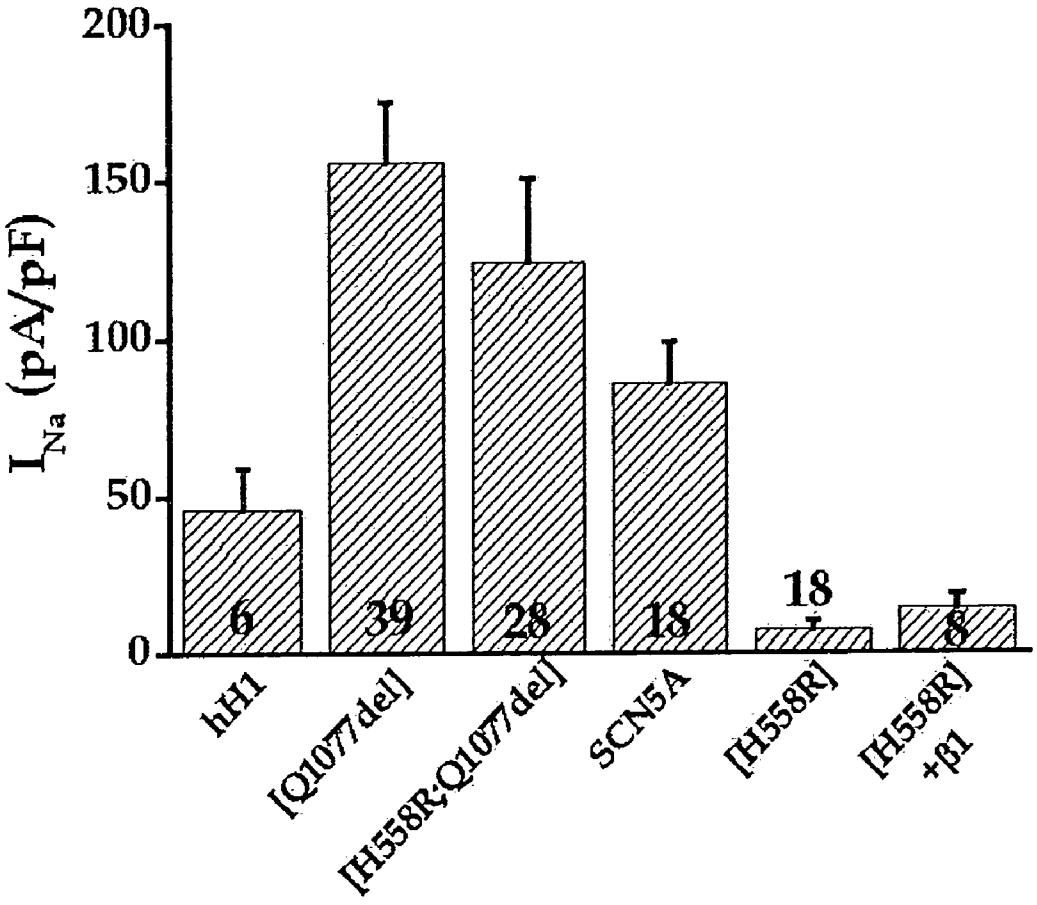

200
150
100
50
0
I_{Na} (pA/pF)
6
39
28
18
18
8
hH1
[Q1077del]
[H558R;Q1077del]
SCN5A
[H558R]
[H558R] +β1

FIG. 5

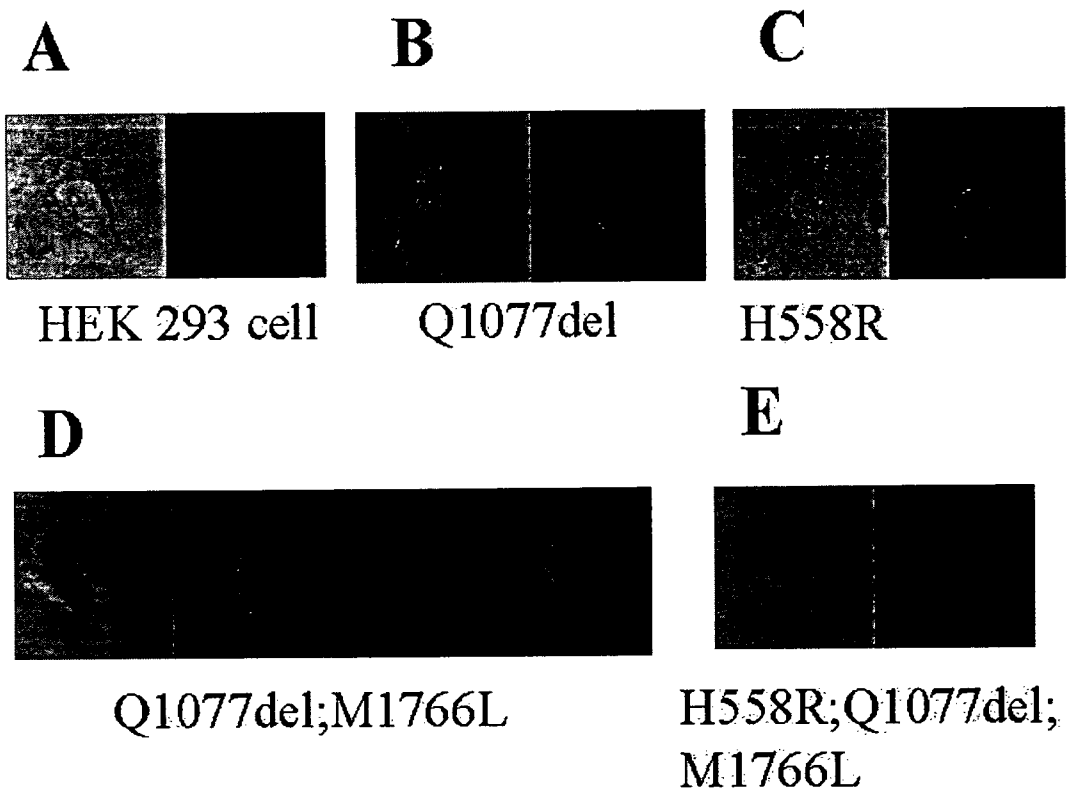

A
B
C
HEK 293 cell
Q1077del
H558R
D
E
Q1077del;M1766L
H558R;Q1077del;
M1766L

FIG. 6

NUCLEIC ACID ENCODING SODIUM CHANNEL SUBUNIT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional application Ser. No. 60/401,018, filed on Aug. 2, 2002, which is incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with United States government support awarded by the following agency: NIH, Grant No. HL56441. The United States government has certain rights in this invention.

BACKGROUND OF THE INVENTION

Sodium channel proteins embedded in cellular membranes of muscle cells, neurons and other excitable cells help produce and propagate electrical impulses and are implicated in many human diseases and conditions. Sodium channels are often composed of a pore-forming α subunit, having four homologous domains DI-DIV and six transmembrane regions S1-S6 per domain, and at least three auxiliary subunits β1, β2 and β3. The α subunit is sufficient to form a functional channel for generating sodium current flow across cellular membranes. An extensive review of cardiac ion channels published in Annual Review of Physiology 64:431-75 (2002) is incorporated by reference in its entirety as if set forth herein.

Human cardiac sodium channels play a critical role in cardiac excitation. $hNa_v1.5$, a human cardiac sodium channel α subunit encoded by the SCN5A gene forms a functioning monomeric sodium channel that carries the inward Na current (I_{Na}) in the heart. The I_{Na} current is vital for excitation and conduction in working myocardium and in specialized conduction tissue such as Purkinje fibers.

Three distinct full-length polymorphic SCN5A clones that encode the hNav1.5 human cardiac sodium channel (designated SCN5A hH1, SCN5A hH1a, and SCN5A hH1b (or simply hH1, hH1a, and hH1b, respectively) have been isolated from human cardiac cDNA libraries (Gellens, M. E. et al., "primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel," *Proc. Natl. Acad. Sci. U.S.A.* 89, 554-558 (1992); Hartmann, H. A. et al., Effects of III-IV linker mutations on human heart Na^+ channel inactivation gating. *Circ. Res.* 75, 114-122 (1994), Ye, B. and J. Makielski, Third Complete Sequence of Human Cardiac Sodium Channel α Subunit Reveals Polymorphism in Domain I and II, Biophys. J. 80(1):225c (2001), each incorporated by reference herein as if set forth in its entirety.).

Subsequent to the publication of the hH1b sequence by Ye and Makielski, the authors determined errors in the published SCN5A hH1 protein sequence. The true polymorphisms among hH1, hH1a and hH1b are reflected in Table 1, infra. The amino acid numbering follows that of the original hH1 clone which contains 2016 amino acids. All of the differences are confined to the cytoplasmic linkers between DI-II and between DII-III. Briefly, hH1 and hH1a differ by just 3 amino acids—T559 vs. A559, Q1027 vs. R1027, and Q1077 vs. Q1077del (hH1 vs. hH1a, respectively)—over a total length of 2016/2015 amino acids, respectively. The hH1b protein also differs from either hH1 or hH1a at positions 559, 1027 and 1077, as well as at positions 558 and 618. The arginine at position 558 in hH1b is consistent with a previously characterized histidine-to-arginine polymorphism (Iwasa, et al., "Twenty single nucleotide polymorphisms (SNPs) and their allelic frequencies in four genes that are responsible for familial long QT syndrome in the Japanese population," *J. Hum. Genet.* 45, 182-183). The isoleucine at position 618 is consistent with a known high-frequency spontaneous conservative leucine-to-isoleucine substitution.

The significance of polymorphisms in the sodium channel is still unknown. For example, it is not known how such polymorphisms affect the mutation phenotype of SCN5A. Nonetheless, identified polymorphisms can help identify disease-associated mutations in SCN5A. For example, various SCN5A mutations are associated with congenital Long QT syndrome, idiopathic ventricular fibrillation and the Brugada syndrome (Keating and Sanguinetti 2001).

In separate studies, the two known polymorphic forms showed only minor kinetic differences that can be attributed to different expression systems and study techniques including solutions, temperature, and protocols. (Gellens, M. E. et al., supra; Hartmann et. al., supra; and Wattanasirichaigoon et. al. 1999). Subtle differences in kinetics such as decay rates, inactivation midpoints, and late I_{Na}, however, may be important in controlling repolarization.

Sodium channel α subunits encoded by an SCN5A hH1a clone carrying an arrhythmogenic missense methionine-to-leucine mutation at amino acid 1766 (M1766L) further exhibit a significant inward sodium current level drop, relative to the current level in channels encoded by a wild type hH1a clone. Recently, M1766L in the hH1a background was shown to have a trafficking defect and to cause QT prolongation and ventricular arrhythmia. These conditions can be rescued by low temperature, antiarrhythmic drugs and the β1 subunit. Valdivia et. al., C. R. et al., A Novel SCN5A Arrhythmia Mutation M1766L with Expression Defect Rescued by Mexiletine," *Cardiovasc. Res.* 54(3):624-9 (2002).

In another aspect, drugs that can alter sodium channel activities can relieve or prevent symptoms of certain conditions such as cardiac arrhythmias. Cardiac arrhythmias are abnormalities in the rate, regularity, or site of origin of the cardiac impulse, or a disturbance in conduction of the impulse that alters the normal sequence of atrial or ventricular activation. One known way to treat cardiac arrhythmias is to block the activity of a cardiac sodium channel. Sodium channel blockers used to treat cardiac arrhythmias include: Quinidine, Lidocaine, Procainamide, Mexiletine, Flecainide, Moricizine, and Disopyramide. Identifying other polymorphic forms of human cardiac sodium channel will advance our understanding of sodium channel-related heart problems and provide new tools for developing diagnostic, prophylactic and therapeutic strategies.

The art is uncertain as to whether any of the three polymorphic SCN5A isolates encodes a standard or reference $hNa_v1.5$ protein. This uncertainty precludes a well-reasoned analysis of mutations at particular amino acid residues in a consistent background. It is important to employ channel proteins having a suitable genetic background when evaluating one or more mutations of interest so that the actual effect of the mutations is noted. In addition, when studying possible direct and indirect drug interactions with cardiac channels, it is important to assess those interactions in the proper context. The full import of the genetic background of mutations in $hNa_v1.5$ has not heretofore been understood.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to novel $hNa_v1.5$ sodium channel α subunit polypeptides designated as SCN5A variants [H558;Q1077], [H558R], [Q1077del] and [H558R; Q1077del], as well as polynucleotides that encode the polypeptides. The novel $hNa_v1.5$ polypeptides differ from the

previously reported hH1, hH1a and hH1b sequences at amino acid positions 559, 618 and 1027.

The present invention is of particular interest in that the art has heretofore presumed that hH1, hH1a or hH1b encoded the "wild-type" or "reference" background sequence against which the effects of various SCN5A mutations should be judged. It is disclosed herein, however, that the disclosed sequences are observed in hundreds of individuals tested, establishing that they are the true standard background sequences in humans. The impact of selecting a proper background sequence when evaluating cardiac sodium channels is demonstrated herein in the Example below by showing the differential effect of a single amino acid change placed upon the background peptides of the invention as opposed to the same change placed upon the prior $hNa_v1.5$ peptides.

The present invention also includes various related nucleic acid molecules and polypeptides that are useful in various applications such as detecting the subunit and generating antibodies to the subunit. The present invention also relates to cloning and expression vectors and cells containing same. In addition, the present invention includes methods for screening for an agent for altering (increasing or reducing) sodium channel activities. Furthermore, methods of using the nucleic acids and polypeptides to detect the SCN5A variants disclosed herein and to generate antibodies to detect and purify the variants are also included in the present invention. New diagnostic and treatment strategies for various sodium channel-related diseases and conditions are also enabled by the present invention. The polypeptides of the SCN5A variants find particular application for use as a background into which putative disease causing mutations are introduced for functional analyses, where the background is more representative of the population than prior human cardiac sodium channels, particularly more representative than hH1, which has been considered a de facto standard channel, even though the inventors have determined that it is not widely distributed in the population at large.

It is an object of the present invention to identify some of the most common forms of a human cardiac sodium channel.

It is another object of the present invention to provide new tools for designing diagnostic and treatment strategies for sodium channel related diseases and conditions.

It is an advantage of the present invention that the SCN5A amino acid sequences are common in the human population.

It is a feature of the present invention that an SCN5A polypeptide of the invention has a threonine at amino acid position 559, a leucine at amino acid position 618, an arginine at amino acid position 1027 and a histidine or arginine at amino acid position 558, and either has a glutamine at amino acid position 1077 or misses the glutamine at the 1077 position due to alternative mRNA splicing. Examples of the polypeptides of the present invention include but are not limited to SEQ ID NO:2, 4, 6 and 8. It is further understood by the inventors that the polypeptides of the invention represent suitable background protein sequences upon which one or more further mutations can be introduced using standard methods known in the art and that use of a polypeptide comprising 20 or fewer amino acid differences from SEQ ID NO:2, 4, 6 or 8 over the length of SEQ ID NO:2, 4, 6 or 8, is within the scope of the invention. More preferably the altered polypeptide comprises 10 or fewer differences, or 5 or fewer, and most preferably a single difference, from SEQ ID NO:2, 4, 6 or 8.

An additional set of polypeptides of the invention further comprise a leucine at position 1766, but otherwise retain the amino acid sequences of the aforementioned set of polypeptides.

In a related aspect, the invention also relates to an isolated polynucleotide that encodes any of the aforementioned polypeptides of the invention. A polynucleotide of the invention can be an isolated nucleic acid molecule such as an mRNA molecule, a single or double stranded DNA molecule or a cDNA molecule, whether or not provided on a cloning vector or expression vector, as well as the complement of any of the foregoing. If the polynucleotide is a nucleic acid molecule provided on an expression vector, it can contain such upstream and/or downstream regulatory elements as are needed to support transcription and translation of the polynucleotide of the invention.

Other objects, advantages and features of the present invention will become apparent from the following specifications and claims.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIG. **1** shows alternative splicing of SCN5A at Exon 18. The top panel shows an example of sequencing data of RT-PCR products from mRNA isolated from human ventricle (see Example below). Note the single sequence present in the Exon 17 coding region, but a dual sequence in the exon 18 coding region. The splice acceptor site in the genomic DNA has two "cag" repeats leading to the alternative splicing of a glutamine at position 1077. This results in two splice variants, one of 2015 amino acids (mRNA top) and one with 2016 amino acids (mRNA bottom).

FIG. **2** shows quantitative analysis of alternatively spliced variant SCN5A transcripts that either encodes Q1077 or excludes Q1077 (Q1077de1). (A) Examples of RT-PCR products from 3 control experiments and 4 subjects. A sample without DNA (NEG) served as a negative control, and synthesized template of 135 bp containing the "cag" repeat (Q1077) and template of 132 bp without the "cag" repeat (Q1077de1) served as positive controls. RT-PCR from samples of mRNA taken at autopsy from a subject with sudden infant death syndrome (SIDS), an infant without structural heart disease (Infant), an adult with no structural heart disease (Adult), and from a myomectomy specimen from a patient with hypertrophic cardiomyopathy (HCM) all show the presence of both transcripts. (B) Summary data from 20 subjects (five in each group) show that the transcript coding for Q1077de1 was consistently more abundant relative to Q1077. Bars represent the mean and standard deviation of the relative abundance of each transcript from 5 subjects determined by autoradiography phosphoimaging.

FIG. **3** shows voltage clamp data for SCN5A variants. Current traces for hH1 and four common SCN5A channel variants sequences are shown. Currents were elicited by step depolarizations from a holding potential of −140 mV to various test potentials of 24 ms duration from −140 mV to +60 mV. No obvious differences in current time course were noted

FIG. **4** shows activation, inactivation and recovery kinetics of SCN5 variants. (A) Summary data of peak current voltage relationships for currents obtained as in FIG. **3**. Data were normalized to the peak I_{Na} in each data set. The lines shown were generated by a Boltzmann function $Gna=[1+\exp(V_{1/2}-V)/K]^{-1}$, where $V_{1/2}$ and K are the mid-point and the slope factor, respectively, and $Gna=I_{Na}/(V-Vrev)$ where Vrev is the reversal potential. (B) Summary data for the voltage dependence of "steady-state" inactivation. I_{Na} obtained in response to a test depolarization to 0 mV from a holding potential of −140 mV, following 1 sec conditioning step to the various conditioning potentials (Vc). In order to normalize the capacity transients a 0.2 ms step back to −140 was applied before a test depolarization. The voltage dependent availability from inactivation relationship was determined by fitting the data to the Boltzmann function: $I_{Na}\ I_{Na\text{-}max}[1+\exp(Vc-V_{1/2})/K]^{-1}$, where the $V_{1/2}$ and K are the midpoint and the slope factor, respectively, and V is the membrane potential. (C) Summary data for recovery from inactiva-

tion was assessed using a two pulse protocol where a conditioning step of 1 sec to 0 mV inactivated I_{Na} followed by a test pulse to 0 mV after a recovery period "t" at a recovery potential of −140 mV. The peak I_{Na} in response to the test pulse was normalized to the maximum peak current and plotted versus "t." This recovery process was fit to the sum of two exponentials: Normalized $I_{Na}[A_f \exp(-t/\tau_f)]+[A_s \exp(-t/\tau_s)]$ where t is the recovery time interval, τ_f and τ_s are the fast and slow time constant, and A_f and A_s are the fraction of the recovery components.

FIG. **5** shows summary data for peak I_{Na} densities for the variants shown. Currents were elicited by a step depolarization to −20 mV from a holding potential of −140 mV and normalized to membrane capacitance. Data for the hH1 clone is included as an historical control. Results for [H558R] coexpressed with the β1 subunit are shown in the rightmost bar. The bars depict the mean and standard error of the mean derived from n measurements with the n for each construct shown within the bar. One way ANOVA (Deg. of freedom 124) with Bonferroni t-test was used to assess significance of differences in these amplitudes. By ANOVA, the I_{Na} density for [H558R] was significantly lower ($p<0.05$) than [Q1077del] and [H558R;Q1077del] but not the Q1077 containing variants hH1 or [H558;Q1077].

FIG. **6** shows that [H558R] has normal trafficking to the cell surface. Standard light photography in the left-most image of each panel is compared with confocal micrographs of human embryonic kidney (HEK) cells with immunostaining against a FLAG epitope inserted into the Na channel. (A) Non-transfected HEK-293 cell shows no immunostaining. (B) The [Q1077del] channel shows normal immunostaining pattern in the periphery and around the nucleus. (C) The [H558R] also shows normal staining pattern indicating that it trafficks to the cell surface. (D) With the mutation M1766L in the [Q1077del] the second image shows immunostaining is confined to a perinuclear location. The third image shows immunostaining with an endoplasmic reticulum marker (see Example below) and the fourth image (where the previous two images are superimposed) shows colocalization of the non-trafficking channel with the endoplasmic reticulum marker. (E) When the M1766L mutation was engineered into the [H558R;Q1077] background, normal trafficking to the cell periphery was seen. All results represented here were seen in at least 7 additional experiments.

DETAILED DESCRIPTION OF THE INVENTION

It is disclosed here that none of the existing SCN5A clones (hH1, hH1a and hH1b) represents a common sequence for SCN5A because each contains a rare variant at one or more of amino acid positions 559, 618 and 1027 (see Table 1). The inventors have identified four groups of SCN5A variants that represent the most common SCN5A variants with regard to the above amino acid positions as well as two additional positions, 558 and 1077. The SCN5A background can be important for the function of disease causing mutations. For example, the Brugada syndrome mutation T1620M showed a trafficking defect only with the relatively uncommon variant R1232W in the background (Baroudi, G. et al., *Circulation Research* 90:E11-E16, 2002). In another example, the H558R background affected the kinetics of the conduction disease mutation T512I (Viswanathan, P C et al., *J. Clin. Invest.* 111:341-346, 2003). In the Example below, M1766L arrhythmia mutation affected SCN5A trafficking only in the [1077del] background but not [H558R;1077del] background. Thus, it is important to study and test disease-causing or potentially disease-causing mutations in a relevant SCN5A background. It is also important to use a relevant SCN5A background for drug screening. Information on SCN5A background of a patient can be important for diagnostic and therapeutic purposes. The disclosure of the most common SCN5A variants here provides new tools to conduct SCN5A-related tests.

All four groups of SCN5A variants identified by the inventors have a threonine at amino acid position 559, a leucine at amino acid position 618 and an arginine at amino acid position 1027. However, they differ at amino acid positions 558 and 1077. Group 1 has a histidine at amino acid position 558 and a glutamine at amino acid position 1077. Group 2 has an arginine at amino acid position 558 and a glutamine at amino acid position 1077. Group 3 has a histidine at amino acid position 558 with the glutamine at amino acid position 1077 deleted. Group 4 has an arginine at amino acid position 558 with the glutamine at amino acid position 1077 deleted. Other positions of the SCN5A variants in these four groups can vary. For example, amino acid position 1103 for all groups can either be a serine (majority of the overall population) or a tyrosine (13.2% of the black population). The expected overall population frequencies for variant groups 1-4 are 24.5%, 10.5%, 45.5% and 19.5%, respectively. An example of an SCN5A amino acid sequence for each of the variant groups 1-4 is provided as SEQ ID NO: 2, 4, 6 and 8, respectively. The corresponding nucleotide sequences are SEQ ID NO:1, 3, 5 and 7, respectively.

The presence or absence of a glutamine at position 1077 is believed to arise from alternative mRNA splicing as part of the normal protein expression process. An individual can be homozygous or heterozygous for histidine or arginine at position 558. Individuals who are heterozygous at position 558 would, therefore, be expected to have all four forms of the $hNa_v1.5$ ion channel. Position 558 is believed to be located at or near a site of protein kinase A (PKA) phosphorylation in $hNa_v1.5$ sodium ion channels, and this amino acid position may play a role in regulation of the channel function.

For purpose of the present invention, the amino acids of the SCN5A variants are numbered by referring to the 2016 amino acid sequence GenBank Accession No. AC137578. Thus, in a variant with a 1077 deletion, the amino acid after amino acid 1076 is numbered 1078 so that the last amino acid is still 2016 instead of 2015. For example, the recently described polymorphism that appears to predispose to ventricular ectopy would be referred to as S1103Y (Chen, S. et al., *J. Med. Genet.* 39:913-915, 2002) rather than "Y1102" (Viswanathan, P C et al., *J. Clin. Invest.* 111:341-346, 2003). Channels with sequence variations from the reference sequence are denoted by the amino acid substitutions separated by semicolons and contained in brackets. Accordingly, SCN5A variant groups 1-4 as disclosed here are referred to as [H558;Q1077], [H558R], [Q1077del], and [H558R;Q1077del], respectively. It is noted that in the attached sequence listing, the amino acids in SEQ ID NO:6 and 8 are numbered under the 2015 system because the PatentIn program automatically numbers the amino acids consecutively.

The term "isolated nucleic acid" or "isolated polypeptide" used in the specification and claims of the present invention means a nucleic acid or polypeptide isolated from its natural environment or prepared using synthetic methods such as those known to one of ordinary skill in the art. Complete purification is not required in either case. Amino acid and nucleotide sequences that flank a polypeptide or polynucleotide that occurs in nature, respectively, can but need not be absent from the isolated form. The polypeptides and nucleic acids of the invention can be isolated and purified from normally associated material in conventional ways such that in the purified preparation the polypeptide or nucleic acid is the predominant species in the preparation. At the very least, the degree of purification is such that the extraneous material in the preparation does not interfere with use of the polypeptide or nucleic acid of the invention in the manner disclosed herein. The polypeptide or nucleic acid is preferably at least

about 85% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Further, an isolated nucleic acid has a structure that is not identical to that of any naturally occurring polynucleotide or to that of any fragment of a naturally occurring genomic polynucleotide spanning more than three separate genes. An isolated nucleic acid also includes, without limitation, (a) a polynucleotide having a sequence of a naturally occurring genomic or extrachromosomal nucleic acid molecule but which is not flanked by the coding sequences that flank the sequence in its natural position; (b) a polynucleotide incorporated into a vector or into a prokaryote or eukaryote genome such that the resulting molecule is not identical to any naturally occurring vector or genomic DNA; (c) a separate molecule such as a cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment; and (d) a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. Specifically excluded from this definition are polynucleotides present in mixtures of clones, e.g., as these occur in a DNA library such as a cDNA or genomic DNA library. An isolated nucleic acid can be modified or unmodified DNA or RNA, whether fully or partially single-stranded or double-stranded or even triple-stranded. A nucleic acid can be chemically or enzymatically modified and can include so-called non-standard bases such as inosine.

In one aspect, the present invention relates to an isolated polypeptide comprising the amino acid sequence of an SCN5A variant disclosed herein. The SCN5A variant can be any SCN5A sequence that has a threonine at amino acid position 559, a leucine at amino acid position 618, an arginine at amino acid position 1027, a histidine or arginine at amino acid position 558, and a glutamine or glutamine deletion at amino acid position 1077. Examples amino acid sequences of an SCN5A variant are provided as SEQ ID NO:2, 4, 6 and 8. Generally speaking, an SCN5A variant of the present invention will not differ from SEQ ID NO:2, 4, 6 or 8 at more than 20 amino acid positions other than positions 558, 559, 618, 1027 and 1077. Preferably, the difference is limited to 10 or fewer, more preferably 5 or fewer, and most preferably 1 or fewer positions. However, it is understood that substitutions such as a conservative substitution can be introduced into non-critical amino acid positions and this will not materially affect the function even when more than 20 amino acids are substituted. An SCN5A variant with such substitutions is within the scope of the present invention.

Furthermore, an isolated polypeptide of the invention can also include one or more amino acids at either or both of the N-terminus and C-terminus of an SCN5A variant disclosed herein, where the additional amino acid(s) do not materially affect the function of the variant, which can be determined using the parameters shown in Table 3. Any additional amino acids can, but need not, have advantageous use in purifying, detecting, or stabilizing the polypeptide. Likewise, small deletions or other rearrangements in the polypeptide that do not affect the function of the polypeptide are also within the scope of the invention. Such deletions are preferably deletions of fewer than 100 amino acids, more preferably of fewer than 50 amino acids, still more preferably of fewer than 10 amino acids.

In a related aspect, the present invention also includes an immunogenic fragment of an SCN5A variant disclosed herein and an antibody that binds specifically to such an immunogenic fragment. Such immunogenic fragments are used to generate specific antibodies that can be used to detect or isolate an SCN5A variant of the present invention, or both. In general, the immunogenic fragments contain at least 15 continuous amino acids, preferably at least 20 continuous amino acids, and most preferably at least 25 continuous amino acids of an SCN5A variant in which the continuous amino acids include position 558. An antibody that is specific for a variant of the present invention will have a higher affinity for the variant than for hH1, hH1a, or hH1b. It is well within the ability of a skilled artisan to make monoclonal or polyclonal antibodies against some or all of the polypeptides and to assess the specificity of the antibodies. Furthermore, as it is now shown by the inventors that the variants disclosed herein are the "common" or "standard" forms of the $hNa_v1.5$ protein, an antibody that merely identifies the protein may be sufficient for various uses, without regard to its specificity relative to hH1, hH1a and hH1b.

In another aspect, the present invention relates to an isolated nucleic acid containing a coding polynucleotide or its complement wherein the coding polynucleotide has an uninterrupted sequence that encodes a polypeptide of the invention as set forth above. A nucleic acid containing a polynucleotide that is at least 80% identical to the coding polynucleotide or its complement over the entire length of the coding polynucleotide can be used as a probe for detecting the coding polynucleotide and is thus within the scope of the present invention.

In a related aspect, any nucleic acid of the present invention described above can be provided in a vector in a manner known to those skilled in the art. The vector can be a cloning vector or an expression vector. In an expression vector, the polypeptide-encoding polynucleotide is under the transcriptional control of one or more non-native expression control sequences which can include a promoter not natively found adjacent to the polynucleotide such that the encoded polypeptide can be produced when the vector is provided in a compatible host cell or in a cell-free transcription and translation system. Such cell-based and cell-free systems are well known to the skilled artisan. Cells comprising a vector containing a nucleic acid of the invention are themselves within the scope of the present invention. Also within the scope of the present invention is a host cell having the nucleic acid of the present invention integrated into its genome at a non-native site. Further, the above cells of the present invention can contain SCN5A variants from more than one of the four variant groups.

The present invention also includes an isolated nucleic acid molecule that contains a fragment of at least 12, 15, 20 or 25 contiguous nucleotides of an SCN5A variant disclosed herein, or its complement, particularly a fragment that comprises codon 558, 1077, or both. Such a nucleic acid molecule can be used to detect the expression of the SCN5A variant in a cell. The detection reaction can be run under stringent hybridization conditions, for example, by hybridizing at 68° C. in 5×SSC/5× Denhardt's solution/1.0% SDS, and washing in 0.2×SSC/0.1% SDS at room temperature. Moderately stringent conditions which include washing in 3×SSC at 42° C. can also be used.

The present invention also enables a screening method for agents that can either inhibit or enhance sodium channel activities. In such a method, an agent is exposed to a host cell of the present invention that expresses one or more SCN5A variants disclosed herein and the agent's effect on the variants' activities is determined by comparing to control cells that are not exposed to the agent. The activity of an SCN5A variant can be measured in many ways, including but not limited to measuring a sodium current across the cell membrane, a sodium current kinetic activity, a membrane potential, or an intracellular sodium level. Agents that can modulate the expression of an SCN5A variant can be screened similarly

using cells which contain the variant whose expression is controlled by the native expression control sequences. Also, a phenotype associated with over-expression of a sodium channel or absence of expression (e.g., in a transgenic or knockout animal) can be monitored. In vitro, an effect on action potential can be measured after a channel of interest is transfected into suitable cells, such as cardiac cells. An arsenal of agents affecting the sodium channel activity is desired because many diseases and conditions, such as arrhythmias and Brugada syndrome, result from elevated or reduced sodium channel activity. Particularly in view of the understanding that various forms of the sodium channel α subunit differ functionally, it is important to evaluate the effects of every form that may be present in an individual. Indeed, one can tailor a suitable treatment to an individual after evaluating the form of a subunit present in that individual. Sodium channel activity means the open channel activity leading to a peak sodium current. Sodium channel activity is enhanced or inhibited when the open state probability is greater or less, and the peak current is higher or lower, respectively, than in the absence of a modulating agent.

The human embryonic kidney cell line (HEK) described in the Example below is a suitable cell line that can be transfected with various SCN5A constructs of the present invention to screen for agents that can affect the function of an SCN5A variant. This cell advantageously lacks endogenous SCN5A proteins to interfere with the signal from a transfected SCN5A of interest. However, other suitable cells can also be used. If a cell, such as a heart cell, which expresses endogenous SCN5A is used, the signal attributable to the endogenous protein must be subtracted when the activity of a transfected SCN5A is measured.

Batteries of agents for screening are commercially available in the form of various chemical libraries including peptide libraries. Examples of such libraries include those from ASINEX (e.g., the Combined Wisdom Library of 24,000 manually synthesized organic molecules) and from CHEMBRIDGE CORPORATION (e.g., the DIVERSet™ library of 50,000 manually synthesized chemical compounds; the SCREEN-Set™ library of 24,000 manually synthesized chemical compounds; the CNS-Set™ library of 11,000 compounds; the Cherry-Pick™ library of up to 300,000 compounds). Once an agent having desired ability to increase or decrease activity of the sodium channel protein is identified, further iterations of the screen using one or more libraries of derivatives of that agent can be screened to identify agents having superior effects.

The above screening methods also enable one to determine the likelihood that an agent intended to be administered to a human or non-human subject will induce an undesired and unintended side effect, namely by altering the activity of the cellular SCN5A in the subject.

The present invention also enables a skilled artisan to determine whether a mutation is associated with a sodium channel-related disease on a common SCN5A background. To do this, a mutation is introduced into an SCN5A variant disclosed herein and the effect of the mutation is then tested in a suitable model for the disease.

The polypeptides, polynucleotides and antibodies of the invention find particular utility as screening tools for identifying to which of the four SCN5A groups a particular subject belongs. This information is useful in several aspects. For example, it may help assess the subject's predisposition to acquired arrythmias. For instance, if a subject has a high proportion of low-expressing channels such as [H558R], the subject could be predisposed to develop acquired arrythmias. Also, for a subject that suffers from a sodium channel-related disease, knowing the SCN5A background of the subject can help choose treatment strategies.

With the disclosure herein, it is well within a skilled artisan's ability to determine to which of the four SCN5A groups a subject belongs. Such determination can be made at the polynucleotide level or protein level. At the polynucleotide level, primers and probes that specifically amplify or hybridize to each of the four SCN5A groups can be used. Alternatively, direct sequencing can also be used. At the protein level, antibodies specific for each of the four SCN5A groups can be developed and used. Alternatively, the amino acid sequence of an SCN5A protein can be determined directly.

Any product of the invention described herein can be combined with one or more other reagent, buffer or the like in the form of a kit useful, e.g., for diagnostic or therapeutic purposes, in accord with the understanding of a skilled artisan.

The present invention is not intended to be limited to the foregoing, but rather to encompass all such variations and modifications as come within the scope of the appended claims. The invention will be more fully understood upon consideration of the following Examples which are, likewise, not intended to limit the scope of the invention.

EXAMPLE

Materials and Methods

Genotyping for residues 558, 559, 618 and 1027: Allele frequencies for the SCN5A variants (H558R in exon 12, T559A in exon 12, L618I in exon 12, and R1027Q in exon 17) were established by direct genomic DNA sequencing of 400 reference alleles derived from the 100 Caucasian human variation panel and the 100 African-American human variation panel (Coriell Cell Repositories and the National Institute of General Medical Sciences). Protein-encoding sequences harboring these variants were amplified by polymerase chain reaction (PCR) using previously published intron/exon based primers 5 and subsequently sequenced using automated dye-terminator cycle sequencing on an ABI Prism 377. The fluorescent detection stems from reporter dyes bound to the ddNTP terminator nucleotides. The Big-Dye Terminator Cycle Sequencing v 1.0 kit from Applied Biosystems (ABI part# 4303154) was used for sequencing of all samples. To determine the status at residues 558, 559, and 618, SCN5A exon 12 was analyzed by PCR amplification of two overlapping fragments 12A (forward primer—GCCAGTGGCTCAAAAGACAGGCT (SEQ ID NO:9) and reverse primer—CCTGGGCACTGGTCCGGCGCA (SEQ ID NO:10)) and 12B (forward primer—CACCACACATCACTGCTGGTGC (SEQ ID NO:11) and reverse primer—GGAACTGCTGATCAGTTTGGGAGA (SEQ ID NO:12)). PCR amplification reactions for amplicons 12A and 12B were performed in 20 μL volumes using 50 ng of genomic DNA, 16 pmol of each primer, 200 μM of each dNTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 2.0 mM $MgCl_2$, and 1.0 U of Amplitaq Gold (Applied Biosystems, Branchburg, N.J.). The reaction mixture was subjected to a 95° C. initial denaturation for 5 min, followed by 5 cycles of 94° C. for 20 s, 64° C. for 20 s, and 72° C. for 30 s; then an additional 35 cycles of 94° C. for 20 s, 62° C. for 20 s, 72° C. for 30 s, and a final extension of 72° C. for 10 min. PCR reactions used to amplify SCN5A exon 17 (R1027Q variant) were performed in 20 μL volumes using 50 ng of genomic DNA, 16 pmol of each primer (forward primer—GCCCAGGGCCAGCTGCCCAGCT (SEQ ID NO:13) and reverse primer—CTGTATATGTAGGTGCCTTATACATG (SEQ ID NO:14)), 200 pM of each dNTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 1.0 mM $MgCl_2$, 8%

DMSO and 1.0 U of Amplitaq Gold (Perkin-Elmer). The cycling conditions were as follows: 94° C. initial denaturation for 10 min, followed by 40 cycles of 94° C. for 30 s, 60° C. for 30 s, 72° C. for 30 s, and a final extension of 72° C. for 10 min. PCR products for exon 12 (12A and 12B) and exon 17 were enzymatically treated to remove unincorporated dNTP and primers with EXOSAP-it (USB Inc., Cleveland, Ohio) following the manufacturer's protocol. Treated products were sequenced using dye-terminator cycle sequencing with an ABI 377, and the resulting chromatograms were analyzed for the specific variant.

Identification, characterization, and quantification of alternatively-spliced SCN5A transcripts encoding for either insertion or deletion of glutamine (Q) at residue 1077: Direct DNA sequencing was performed on exon 17/18 targeted RT-PCR generated products derived from messenger RNA that was extracted from myocardial tissue obtained at either i) autopsy of sudden infant death syndrome (n=5), non-accidental infant death (n=5), or accidental adult death victims (n=5) or ii) surgical myectomy in adults with hypertrophic cardiomyopathy (n=5). Total RNA from an approximate 25 mg piece of heart tissue was isolated using the Rneasy™ Fibrous Tissue Mini kit (Qiagen, Valencia, Calif.), and first-strand cDNA synthesis was performed in triplicate on 500 ng of total RNA using the iScript™ cDNA Synthesis kit (BioRad, Hercules, Calif.) following the manufacturer's specifications. PCR was performed in 20 μL volumes using 2 μL of cDNA, 16 pmol of each primer (17F forward: CCAAGAAGAGGATGAGGAGA (SEQ ID NO:15),18R reverse: GAGGCAGTCGCTGACACC (SEQ ID NO:16)), 200 μM of each dNTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 2.0 mM $MgCl_2$, and 1.0 U Amplitaq Gold (Perkin-Elmer). The cycling conditions were as follows: 94° C. initial denaturation for 10 min, followed by 35 cycles of 94° C. for 30 s, 58° C. for 30 s, 72° C. for 30 s, and a final extension of 72° C. for 10 min. PCR products were purified with EXOSAP-it (USB Inc., Clevland, Ohio) and sequenced using an automated AB1377 sequencer (Applied Biosystems, Inc., Foster City, Calif.). The relative quantity of the 2 alternatively-spliced transcripts was then quantified. Triplicate cDNA samples from each case were subject to PCR amplification using the same PCR primers and conditions as above, with the addition of 0.2 μl of alpha-^{32}P dCTP (10 mCi/ml). Since all samples were shown to harbor both transcripts by direct DNA sequencing, control templates representing homozygous Q1077 and Q1077del transcripts were synthesized and PAGE purified by Integrated DNA technologies, Inc. (Coralville, Iowa). The resulting radionucleotide incorporated PCR products representing 1) the transcript (135 base pairs) encoding the insertion of glutamine at residue 1077 (Q1077) or 2) the transcript (132 base pairs) that does not encode for glutamine at residue 1077 (Q 1077del) were separated by denaturing gel electrophoresis at 70 watts for 2 hrs and 45 min on a 6% polyacrylamide (19:1), 7 M urea gel. Autoradiography with a phosphoimager 445 SI and ImageQuant v 5.0 software (Molecular Dynamics, Piscataway, N.J.) were used for signal quantification of the two alternatively-spliced transcripts.

Gene expression, mutagenesis, and nomenclature: The SCN5A clone hH1 (GenBank No. M77235) was kindly provided by Dr. Al George (Gellens, M E et al., *Proc. Natl. Acad. Sci. U.S.A* 89:554-558, 1992, which is herein incorporated by reference in its entirety) in prcCMV (Invitrogen). The hH1c construct (GenBank No. AY148488) was made from the hH1b clone (GenBank AF482988) (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003, which is herein incorporated by reference in its entirety) by mutating the arginine (R) at 558 to histidine (H), and the isoleucine (I) at positions 618 to leucine (L) by methods described below. The consensus reference sequence (GenBank No. NM_000335 June 2003) has 2015 amino acids and is identical to hH1c. For naming and reference purposes we prefer the full-length 2016 amino acid deduced sequence from the IHGSC (GenBank No. AC137587, deposited April 2003) as the base sequence for SCN5A because this nomenclature retains the well-established numbering system based upon the 2016 amino acids encoded by the original SCN5A clone hH1 (Gellens, M E et al., *Proc. Natl. Acad. Sci. U.S.A* 89:554-558, 1992). Channels with sequence variations from the reference sequence are denoted by the amino acid substitutions separated by semicolons and contained in brackets as recommended by den Dunnen and Antonarakis (den Dunnen, J T et al., *Hum. Mutat.* 15:7-12, 2000). The variant channels [H558R], [Q1077del1], [H558R;Q1077del1], [H558R;Q1077del1;M1766L], and [Q1077del1;M1766L] were made by mutagenesis at appropriate residues by the following method.

Mutations were generated using Excite® mutagenesis kit (Stratagene, La Jolla, Calif.) using the protocol suggested by the manufacturer. DNA was isolated and purified with the Qiagen (Valencia, Calif.) column and protocol. All constructs were sequenced to verify incorporation of the intended amino acid change and to confirm that no unwanted changes were introduced. These constructs were placed in pcDNA3 (Invitrogen, Carlsbad, Calif.) and expressed in HEK293 cell line by transfection with 1.5 μg of plasmid DNA using Superfect (Qiagen) according to the protocol recommended by the manufacturer. A GFP protein was co-transfected (at 1:10) as a marker to identify the transfected cells. HEK 293 cells were harvested 24 hours after transfection to measure macroscopic current as previously described (Nagatomo, T. et al., *Am. J. Physiol.* (*Heart* 44) 275:H2016-H2024, 1998, incorporated by reference in its entirety). Experiments were done with transient transfection unless otherwise noted. A few experiments used cell lines expressing these variants in a stable manner. For these stable cell lines, pcDNA3 (Invitrogen) plasmid DNA containing the hNav1.5 α subunit was transfected into HEK-293 cells and selected as follows. Approximately 1×10^5 cells were plated on a 60 mm diameter plate (Falcon 3001) approximately 24 hours prior to transfection in 3 mL MEM-complete media (Minimal Essential Media (Gibco/Invitrogen) supplemented with 2 mM L-glutamine, 10% Fetal Bovine Serum, 1 mM sodium pyruvate solution, 0.1 mM non-essential amino acids, 10,000 U of Penicillin and 10,000 mg of streptomycin). 1.5 μg of plasmid DNA was mixed along with 10 μL of Superfect reagent (Qiagen) into 140 μL of Opti-MEM (Gibco/Invitrogen) and allowed to incubate at room temperature for 10 min to allow for the DNA to bind to the Superfect. The HEK cells were then incubated with this DNA and Superfect solution in 1 mL MEM-complete for 3.5 hrs, at which point the media was replaced with 3 mL of MEM-complete. 24 hours post-transfection 800 ng/mL of G418 antibiotic was added. MEM-complete+G418 medium was thereafter replaced every 72 to 96 hours. After 3-4 weeks, single colonies were isolated from the transfected plate and grown in separate wells of a 6-well plate (Costar 3516, Corning, N.Y.). RNA was isolated (RNAisol from LPS, Moonachie, N.J.) and screened by RT-PCR analysis. Colonies that tested RT-PCR-positive were then analyzed by voltage clamp.

Voltage-clamp techniques: The whole cell patch-clamp technique was utilized to measure macroscopic I_{Na} (Nagatomo, T. et al., *Am. J. Physiol.* (*Heart* 44) 275:H2016-H2024, 1998). The pipette solution contained 120 mM CsF, 15 mM CsCl, 2 mM EGTA, 5 mM HEPES and 5 mM NaCl (pH7.4 with CsOH). Data were recorded at room temperature

using pCLAMP 8 (Axon Instruments). The voltage-clamp protocols are described briefly with the data and have been published previously in detail (Valdivia, C R et al., *J. Mol. Cell Cardiol.* 34:1029-1039, 2002). Peak I_{Na} and late I_{Na} were obtained after passive leak subtraction as described previously (Nagatomo, T. et al., *Am. J. Physiol.* (*Heart* 44) 275: H2016-H2024, 1998). Parameter fits were obtained using Clampfit 8 (Axon Instruments). One way ANOVA was performed to determine statistical significance among 3 or more groups of mean data. Statistical significance was determined by a P value<0.05.

Immunocytochemistry: The FLAG epitope was introduced between S1 and S2 in domain I for channels used in the immunocytochemistry experiments. Transfected and non-transfected HEK293 cells were fixed with 4% paraformaldehyde at room temperature for 20 minutes. The fixed cells were blocked with 5% goat serum and 0.2% Triton PBS solution at room temperature for 30 minutes. After the blocking procedure, the cells were incubated with the mouse anti-FLAG M2 primary antibody (Stratagene®, La Jolla, Calif.) at the ratio of 1:2000 overnight at 4° C. On the next day, the cells were washed with PBS before 1:100 fluorescein-conjugated goat anti-mouse antibody (Jackson, West Grove, Pa.) was applied as the secondary antibody and allowed to react for 1 hour at room temperature in the dark. The rabbit anti-Calnexin IgG was used as endoplasmic reticulum (ER) marker to test for co-localization. A 1:1000 dilution of the rabbit anti-Calnexin IgG in 250 μl was applied to transfected cells immediately after incubation with fluorescein-conjugated goat anti-mouse secondary antibody. The reaction was incubated for 2 hrs at 37° C. After incubating with anti-Calnexin IgG, the cells were washed twice with 300 μl of PBS and incubated with 150 μl of Texas Red-conjugated goat anti-rabbit secondary antibody (Jackson, West Grove, Pa.) at the ratio of 1:100. The incubation with Texas Red-conjugated goat anti-rabbit 2nd antibody was done at room temperature in the dark for 1 hour. The cells were washed with PBS solution and fixed with a solution containing 90% glycerol and 10% Na carbonate. A Bio-Rad MRC 1024 Laser Scanning system with 15 mW mixed gas (Krypton/Argon) laser was utilized to view immunofluorescently labeled cells. The Bio-Rad MRC 1024 system was mounted on a Nikon Diaphot 200 inverted microscope. Images of the fluorescent-labeled cells were scanned under 40× objective and 2× zoom. The confocal system was set to 3.6 for iris, laser power at 100% and camera sensitivity gain to 900. A Kalman collection filter with 5 frames per image was applied to record the image.

Results

Sequence comparisons for SCN5A clones and genotyping of control panels: The sequences of hH1 (Gellens, M E et al., *Proc. Natl. Acad. Sci. U.S.A* 89:554-558, 1992), hH1a (Hartmann, H A et al., *Circulation Research* 75:114-122, 1994, which is herein incorporated by reference in its entirety), and hH1b (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003) were compared and the amino acid differences at 5 residues are shown in Table 1 along with the GenBank Accession number where available. In a previous study of the hH1b clone (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003), hH1 and hH1a were re-sequenced and the differences between these two clones were found to be only the 3 residues shown in Table 1 rather than the 9 reported previously.

TABLE 1

Comparisons for deduced SCN5A/Na_v 1.5 sequences from full-length cDNA clones (hH1, hH1a, hH1b), genomic sequencing (hH1c) and genomic databases (Celera, 1HGSC).

SCN5A Variant Group		1	2			3	4
Common[a] Name		IHGSC		hH1	hH1a	hH1b	hH1c[d]	
Accession No.[b]		AC137587	NA	M77235	NA	AF482988	AY148488	NA
AA[c] No.	558	R	R	H	H	R	H	R
	559	T	T	T	A	T	T	T
	618	L	L	L	L	I	L	L
	1027	R	R	Q	R	R	R	R
	1077	Q	Q	Q	Δ	Δ	Δ	Δ
Variant[e] name		[H558; Q1077]	[H558R]	[R1027Q]	[T559A; Q1077del]	[H558R; L618I; Q1077del]	[Q1077del]	[H558R; Q1077del]
Population[f] Frequency		24.5%	10.5%	0%	0%	0%	45.5%	19.5%

[a]IHGSC = International Human Genome Sequencing Consortium sequence and reference sequence; hH1, hH1a, hH1b = previously cDNA clones of SCN5A; hH1c = Common sequence from genomic sequencing in control subjects (a search of Celera human genome database identified the same sequence).

[b]Accession No. = GenBank Nucleotide accession numbers, where available.

[c]AA No. = Amino Acid residue number in the protein, using the full length numbering consistent with the IHGSC database as well as the originally isolated SCN5A. At all 2011 the positions not noted in the table above the amino acids are identical in all sequences. "Δ" indicates there is no amino acid present at this location in the amino acids (thus, the product is 2015 amino acids in length, rather than 2016). The amino acid frequencies in the population ofall proteins in the population of all studied humans at positions 558, 559, 618, 1027 and 1077 are 70% H, 100% T, 100% L, 100% R and 65% Δ, respectively.

[d]A search of Celera human genome database identified the same sequence

[e]Variant name = name relative to [H558; Q1077] (defined herein as identical to IHGSC).

[f]Population Frequency = estimated percentage of protein products in the study population that have this sequence.

We investigated allelic frequencies from genomic DNA at the 5 positions in question from a panel of 200 human controls (100 white subjects and 100 black subjects). The most common residues at these 5 positions are reported as hH1c in Table 1. For positions 559, 618, and 1027, 100% of the 400 reference alleles showed T559, L618, and R1027, indicating that each of the existing clones contained a rare variant and that none represented the common sequence (Table 1). A search of the Celera human genome database showed that the deduced amino acid sequence agreed with hH1c. The deduced amino acid sequence in the NIH International Human Genome Sequencing Consortium (IHGSC) also agreed with the hH1c sequence. However, the IHGSC sequence contains the additional glutamine (Q) at position 1077 as found in the hH1 clone but not hH1a or hH1b.

A common polymorphism, H558R: Residue 558 hosts the common polymorphism involving a substitution of histidine (H) with arginine (R)H558R (Iwasa, H. et al., *J. Hum. Genet.* 45:182-183, 2000) with a reported frequency in the population of 19-24% (Yang, P. et al., *Circulation* 105:1943-1948, 2002). We confirm that H558R is a common polymorphism (Table 2) among both blacks and whites; the apparent higher incidence of H558R in blacks is not statistically significant. We also show the frequency of heterozygosity and homozygosity at this position (Table 2).

TABLE 2

Genotype and Allelic Frequency of H558R Polymorphism

Ethnicity	Sample Size	HH	HR	RR	H allele	R allele
White	100	65	30	5	0.8	0.2
Black	100	53	40	7	0.73	0.27

A common alternatively-spliced variant, Q1077del: The hH1 clone contained a glutamine (Q) residue at both amino acid positions 1076 (the final codon of exon 17) and 1077 (the first codon of exon 18) (Gellens, M E et al., *Proc. Natl. Acad. Sci. U.S.A* 89:554-558, 1992). The acceptor site sequence for exon 18 was annotated as ggggtcttttcagCAGGAATCC (SEQ ID NO:17) where the lower case letters represent the intronic sequences and the upper case letters represent the 5' exonic sequences of exon 18 (see FIG. **1**). The underlined lower case letters indicate the predicted "ag" acceptor site rule for splice site recognition. However, splice-site analytical tools indicate that the CAG following the ag shown above could also comprise the terminal intronic sequence and may be the preferred acceptor site for splicing, resulting in a deletion of glutamine at residue 1077 (Q1077del).

To answer the question whether SCN5A most commonly has a glutamine (Q) at both amino acid positions 1076 and 1077 as in hH1 or only 1076 as in hH1a and hH1b, we performed direct sequencing on exon 17/18-targeted RT-PCR generated products derived from mRNA isolated from human left ventricular myocardial specimens from sudden infant death syndrome (SIDS), infants with structurally normal heart, adults with hypertrophic cardiomyopathy, and adults with structurally normal hearts. All subjects were heterozygous for a "cag" in-frame insertion indication the universal presence of alternative-splicing involving this acceptor site (FIG. **1**). The relative abundance for each alternatively-spliced transcript was quantified by autoradiography and phosphoimaging (FIG. **2**). Examples of RT-PCR products generated from myocardial RNA (FIG. **2**A) show the expected size products for control experiments with the 135 bp template containing the extra cag codon (Q1077) and for the 132 bp template lacking the extra cag codon (Q1077del). Summary data (FIG. **2**B) show that Q1077del was the preferred alternatively-spliced variant being significantly more abundant in every group tested. Overall, the proportion of alternatively-spliced variant containing Q1077 was 35±2.0% (range 31-38%, n=20) and the Q1077del transcript was 65±2.0% (range 62-69, n=20). The total test group contained 9 males and 11 females, and the infant group contained 5 white and 5 black subjects. This degree of preferential splicing was not influenced by age, sex, race, or presence of ventricular hypertrophy. In addition, these ratios of Q1077 and Q1077del-transcripts were maintained regardless of whether RNA was obtained from right atrium, left atrium, right ventricle, or left ventricle.

Four common SCN5A variants in the human population: Based upon the predicted amino acid frequency estimates from our genomic sequencing in controls and our measurement of the frequency of the splice variant Q1077del, we estimated the population frequency of the existing clones and other full-length sequences (Table 1). These estimates assume independence between the probability of the Q1077del splice variant (65%) and the genomic variant containing H558R (30%). Note that the three clones hH1, hH1a, and hH1b used in previous studies are estimated to have a very low frequency in the population because of the presence of a rare variant in each. The most common variant [Q1077del] at 45.5% is identical to the hH1c sequence, the Celera sequence, and also to the NCBI Reference Sequence for SCN5A (GenBank Accession number NM_000335). The full-length reference sequence SCN5A ([H558;Q1077]) is actually less frequent than [Q1077del] at 24.5%. Only slightly less common are the variants with the H558R polymorphism designated as [H558R;Q1077del] at 19.5% and [H558R] at 10.5% (by our convention, the [H558R] variant contains Q1077).

Functional characterization of SCN5A variants: Constructs for expressing [H558;Q1077] and the other common variants [H558R], [Q1077del] and [H558R;Q1077del] were made and transfected individually into HEK cells for kinetic studies. For comparison, we expressed hH1 contemporaneously under the same conditions with these variants because most previous studies in the literature have used hH1. Representative currents for the four variants and hH1 are shown in FIG. **3**. For those variants that expressed robust current, no significant differences were identified in i) the parameters of activation (FIG. **4**A, Table 3), ii) current decay (Table 3), iii) recovery from inactivation (FIG. **4**C, Table 3) and iv) late or persistent currents (Table 3). The midpoint of inactivation for hH1, however, was significantly negative to the two variants lacking Q1077 [Q1077del] and [H558R;Q1077del] (FIG. **4**B and Table 3).

TABLE 3

Voltage-dependent Kinetic Parameters for hNa$_v$1.5 Channels

	hH1	[Q1077del]	[H558R; Q1077del]	[H558; Q1077]
		Activation		
$V_{1/2}$ (mV)	−40 ± 2	−42 ± 1.2	−44 ± 2	−40 ± 2
Slope factor	5.5 ± 0.3	4.9 ± 0.1	5.1 ± 0.2	4.9 ± 0.3
N	5	22	23	13
		Inactivation		
$V_{1/2}$ (mV)	−92 ± 2*	−85 ± 1.2	−84 ± 1.3	−85 ± 4
N	18	26	14	5

TABLE 3-continued

Voltage-dependent Kinetic Parameters for $hNa_v1.5$ Channels

	hH1	[Q1077del]	[H558R; Q1077del]	[H558; Q1077]
		Recovery		
τ_f(ms)	3.0 ± 2	2.6 ± 0.3	2.8 ± 0.4	3.3 ± 1.6
τ_s (ms)	81 ± 77	34 ± 4.7	53 ± 14	71 ± 40
A_s	22 ± 0.1	22 ± 0.5	17 ± 2	26 ± 0.9
N	7	19	14	4
		Decay (−30 mV)		
τ_f(ms)	1.8 ± 0.8	1.3 ± 0.4	1.6 ± 0.6	1.0 ± 0.2
τ_s (ms)	11.4 ± 9.6	4.7 ± 3	8.1 ± 8.8	4.0 ± 2.0
A_f	0.64 ± 0.3	0.56 ± 0.2	0.64 ± 0.2	0.7 ± 0.2
N	8	4	6	5
		Late I_{Na} (−20 mV)		
% of peak I_{Na}	—	0.85 ± 0.3	0.43 ± 0.2	0.85 ± 0.3
N	—	10	7	9

The data shown here are the mean ± SEM from curve fitting to N experiments.

Activation, inactivation, and recovery from inactivation parameters were obtained as in FIG. 3.

For the decay of I_{Na} at −30 mV, the portion of the I_{Na} trace after 90% of peak was fit a sum of exponentials: $I_{Na}(t) = 1 - (Af * \exp - t/\tau_f + A_s * \exp - t/\tau_s)$ + offset where t is time, τ_f and τ_s represent the time constant of the fast and slow components, and A_f and A_s are amplitudes of fast and slow component, respectively.

Late I_{Na} was obtained at 720 ms after the depolarization as described previously (Valdivia, CR et al., J. Mol. Cell Cardiol. 34: 1029–1039, 2002).

Using one-way ANOVA with Bonferroni T-test, the midpoint of inactivation for hH1 marked by an asterisk was significantly negative to the variants lacking Q [H558R; Q1077del] and [Q1077del].

The most dramatic finding was that [H558R] which contains Q1077 expressed very low current density. Data for current density are summarized in FIG. **5** where the current density for [H558R] was dramatically and significantly lower than the other variants. Other constructs that contained Q1077 (hH1 and [H558;Q1077]) also tended to have reduced currents but the difference did not reach statistical significance by ANOVA. RT-PCR of mRNA from cells with both transient and stable transfection of [H558R] showed abundant [H558R] transcript, but negligible currents. The #1 subunit increased current density when co-expressed with the α subunit of Nav1.5 (Nuss, H B et al., *J. Gen. Physiol.* 106: 1171-1191, 1995). The β1 subunit also "rescued" the trafficking defective SCN5A mutations (Valdivia, C R et al., *Cardiovascular Research* 54:624-629, 2002). When [H558R] was co-expressed with the β1 subunit, increased currents were observed although not at the levels of the other channel a subunits expressed alone (FIG. **5**). To determine if the small currents seen with [H558R] could be endogenous currents, we voltage clamped untransfected HEK cells. In 8 cells, only 1 cell had 100 pA of current for an average density of less than 0.5 pA/pF compared with 2.8 pA/pF in [H558R] alone and 16 pA/pF in [H558R] co-transfected with the β1 subunit. We were unable to significantly increase endogenous currents in untransfected cells by co-transfection with β1 (1.0±0.5 pA/pF, n=9), incubation with mexiletine 100 μM for 24 hours (1.1±0.4 pA/pF, n=10), or incubation at 27° C. (0.9+0.4 pA/pF, n=8). We conclude that [H558R] did indeed generate small currents. When both variants [H558R] and [H558R; Q1077de1] were co-expressed (plasmid DNA 0.75 μg each), normal current densities were seen. We conclude that variants containing Q1077 tended to have lower I_{Na} density, and also tended to have the voltage-dependence of inactivation kinetics shifted in the negative direction. When the H558R polymorphism is expressed in the setting of the alternatively-spliced transcript that contains Q1077, then I_{Na} density was dramatically reduced.

Cell trafficking of the [H558] variant: Some SCN5A variants with decreased current density have been shown by immunocytochemistry to have defective trafficking (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003; Baroudi, G. et al., *Circulation Research* 90:E11-E16, 2002) and do not make it to the cell surface. To determine if [H558R] made it to the cell surface, we labeled the channel variants by inserting a FLAG epitope, and localized the channels by immunofluorescence and confocal microscopy. In each panel of FIG. **6** a light microscopy image is shown allowing for identification of the nucleus and the cell surface, followed by the confocal immunofluorescence image(s). A non-transfected cell gave no fluorescent signal as expected (FIG. **6**A). The [Q 1077de1] variant that gave robust current densities showed a rim of fluorescence at the cell surface as expected for a normally trafficking channel (FIG. **6**B). The [H558R] variant expressed almost no current, but also showed fluorescence at the cell surface (FIG. **6**C) suggesting that the lack of current was not caused by a trafficking defect.

As an example of a channel that is trafficking defective and as a positive non-trafficking control for our experiment with the [H558R] variant, we made the mutation M1766L in the variants and show data from two of these experiments (FIGS. **6**D & E). We had previously shown M1766L to be trafficking defective in hH1a [T559A;Q1077de1;M1766L] but to be normally trafficking in hH1b [H558R;L6181;Q1077de1; M1766L] (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003). When the M1766L mutation was put into [Q1077de1] to make [Q1077de1;M1766L] (FIG. **6**D), the fluorescence was restricted to the area around the nucleus without any labeling in the periphery, consistent with a trafficking defect. This eliminates the possibility that the rare variant T559A in hH1a was responsible for the trafficking defect as previously described (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003). An image with a marker for the endoplasmic reticulum is shown in the third panel of FIG. **6**D, and the fourth image in FIG. **6**D superimposes the second and third image to show co-localization of the channel with the endoplasmic reticulum marker. When M1766L was placed in the [H558R; Q1077de1] background, the channel is rescued and makes it to the cell periphery (FIG. **6**E), consistent with previous data and also showing that the rare variant L6181 in hH1b was not responsible for "rescuing" the trafficking defect.

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            20                  25                  30

gcc cgc ggc tca acc acc ttg cag gag agc cga gag ggg ctg ccc gag      144
Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
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gag gag gct ccc cgg ccc cag ctg gac ctg cag gcc tcc aaa aag ctg      192
Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
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cca gat ctc tat ggc aat cca ccc caa gag ctc atc gga gag ccc ctg      240
Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
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Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

aat aaa ggc aag acc atc ttc cgg ttc agt gcc acc aac gcc ttg tat      336
Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
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gtc ctc agt ccc ttc cac ccc atc cgg aga gcg gct gtg aag att ctg      384
Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

gtt cac tcg ctc ttc aac atg ctc atc atg tgc acc atc ctc acc aac      432
Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
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tgc gtg ttc atg gcc cag cac gac cct cca ccc tgg acc aag tat gtc      480
Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

gag tac acc ttc acc gcc att tac acc ttt gag tct ctg gtc aag att      528
Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

ctg gct cga ggc ttc tgc ctg cac gcg ttc act ttc ctt cgg gac cca      576
Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

tgg aac tgg ctg gac ttt agt gtg att atc atg gca tac aca act gaa      624
Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

ttt gtg gac ctg ggc aat gtc tca gcc tta cgc acc ttc cga gtc ctc      672
Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
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Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

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Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
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Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
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Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
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Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

gag ggc tac cgg tgc cta aag gca ggc gag aac ccc gac cac ggc tac     1056
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Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

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Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
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tcc ttc tac ctg gtg aac ctg atc ctg gcc gtg gtc gca atg gcc tat     1248
Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
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Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

cgc ttc cag gag gcc atg gaa atg ctc aag aaa gaa cac gag gcc ctc     1344
Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
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acc atc agg ggt gtg gat acc gtg tcc cgt agc tcc ttg gag atg tcc     1392
Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
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cct ttg gcc cca gta aac agc cat gag aga aga agc aag agg aga aaa     1440
Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

cgg atg tct tca gga act gag gag tgt ggg gag gac agg ctc ccc aag     1488
Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

tct gac tca gaa gat ggt ccc aga gca atg aat cat ctc agc ctc acc     1536
Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
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cgt ggc ctc agc agg act tct atg aag cca cgt tcc agc cgc ggg agc     1584
Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

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Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

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545                 550                 555                 560

ctg ctg gtg ccc tgg ccc ctg cgc cgg acc agt gcc cag gga cag ccc     1728
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Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
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cca gag gcc aca tcc cca gga agc cac ctc ctc cgc cct gtg atg cta     1872
Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
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Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

cag atg ctg acc tcc cag gct ccg tgt gta gat ggc ttc gag gag cca     1968
Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
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gga gca cgg cag cgg gcc ctc agc gca gtc agc gtc ctc acc agc gca     2016
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Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
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Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
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Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
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ggg aac tca gtg ggg gca ctg ggg aac ctg aca ctg gtg cta gcc atc     2544
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865                 870                 875                 880

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Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

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Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

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945                 950                 955                 960

ctg gcc ctg gcc cgc atc cag agg ggc ctg cgc ttt gtc aag cgg acc     2928
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            980                 985                 990

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Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
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Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
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cac agc  tgg ttc gag aca ttc  atc atc ttc atg atc  cta ctc agc      3654
His Ser  Trp Phe Glu Thr Phe  Ile Ile Phe Met Ile  Leu Leu Ser
    1205                1210                1215

agt gga  gcg ctg gcc ttc gag  gac atc tac cta gag  gag cgg aag      3699
Ser Gly  Ala Leu Ala Phe Glu  Asp Ile Tyr Leu Glu  Glu Arg Lys
    1220                1225                1230

acc atc  aag gtt ctg ctt gag  tat gcc gac aag atg  ttc aca tat      3744
Thr Ile  Lys Val Leu Leu Glu  Tyr Ala Asp Lys Met  Phe Thr Tyr
    1235                1240                1245

gtc ttc  gtg ctg gag atg ctg  ctc aag tgg gtg gcc  tac ggc ttc      3789
Val Phe  Val Leu Glu Met Leu  Leu Lys Trp Val Ala  Tyr Gly Phe
    1250                1255                1260

aag aag  tac ttc acc aat gcc  tgg tgc tgg ctc gac  ttc ctc atc      3834
Lys Lys  Tyr Phe Thr Asn Ala  Trp Cys Trp Leu Asp  Phe Leu Ile
    1265                1270                1275

gta gac  gtc tct ctg gtc agc  ctg gtg gcc aac acc  ctg ggc ttt      3879
Val Asp  Val Ser Leu Val Ser  Leu Val Ala Asn Thr  Leu Gly Phe
    1280                1285                1290

gcc gag  atg ggt ccc atc aag  tca ctg cgg acg ctg  cgt gca ctc      3924
Ala Glu  Met Gly Pro Ile Lys  Ser Leu Arg Thr Leu  Arg Ala Leu
    1295                1300                1305

cgt cct  ctg aga gct ctg tca  cga ttt gag ggc atg  agg gtg gtg      3969
Arg Pro  Leu Arg Ala Leu Ser  Arg Phe Glu Gly Met  Arg Val Val
    1310                1315                1320

gtc aat  gcc ctg gtg ggc gcc  atc ccg tcc atc atg  aac gtc ctc      4014
Val Asn  Ala Leu Val Gly Ala  Ile Pro Ser Ile Met  Asn Val Leu
    1325                1330                1335

ctc gtc  tgc ctc atc ttc tgg  ctc atc ttc agc atc  atg ggc gtg      4059
Leu Val  Cys Leu Ile Phe Trp  Leu Ile Phe Ser Ile  Met Gly Val
    1340                1345                1350

aac ctc  ttt gcg ggg aag ttt  ggg agg tgc atc aac  cag aca gag      4104
Asn Leu  Phe Ala Gly Lys Phe  Gly Arg Cys Ile Asn  Gln Thr Glu
    1355                1360                1365

gga gac  ttg cct ttg aac tac  acc atc gtg aac aac  aag agc cag      4149
Gly Asp  Leu Pro Leu Asn Tyr  Thr Ile Val Asn Asn  Lys Ser Gln
    1370                1375                1380

tgt gag  tcc ttg aac ttg acc  gga gaa ttg tac tgg  acc aag gtg      4194
Cys Glu  Ser Leu Asn Leu Thr  Gly Glu Leu Tyr Trp  Thr Lys Val
    1385                1390                1395

aaa gtc  aac ttt gac aac gtg  ggg gcc ggg tac ctg  gcc ctt ctg      4239
Lys Val  Asn Phe Asp Asn Val  Gly Ala Gly Tyr Leu  Ala Leu Leu
    1400                1405                1410

cag gtg  gca aca ttt aaa ggc  tgg atg gac att atg  tat gca gct      4284
Gln Val  Ala Thr Phe Lys Gly  Trp Met Asp Ile Met  Tyr Ala Ala
    1415                1420                1425

gtg gac  tcc agg ggg tat gaa  gag cag cct cag tgg  gaa tac aac      4329
Val Asp  Ser Arg Gly Tyr Glu  Glu Gln Pro Gln Trp  Glu Tyr Asn
    1430                1435                1440

ctc tac  atg tac atc tat ttt  gtc att ttc atc atc  ttt ggg tct      4374
Leu Tyr  Met Tyr Ile Tyr Phe  Val Ile Phe Ile Ile  Phe Gly Ser
    1445                1450                1455

ttc ttc  acc ctg aac ctc ttt  att ggt gtc atc att  gac aac ttc      4419
Phe Phe  Thr Leu Asn Leu Phe  Ile Gly Val Ile Ile  Asp Asn Phe
    1460                1465                1470

aac caa  cag aag aaa aag tta  ggg ggc cag gac atc  ttc atg aca      4464
Asn Gln  Gln Lys Lys Lys Leu  Gly Gly Gln Asp Ile  Phe Met Thr
    1475                1480                1485
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gag gag  cag aag aag tac tac  aat gcc atg aag aag  ctg ggc tcc      4509
Glu Glu  Gln Lys Lys Tyr Tyr  Asn Ala Met Lys Lys  Leu Gly Ser
    1490                 1495                 1500

aag aag  ccc cag aag ccc atc  cca cgg ccc ctg aac  aag tac cag      4554
Lys Lys  Pro Gln Lys Pro Ile  Pro Arg Pro Leu Asn  Lys Tyr Gln
    1505                 1510                 1515

ggc ttc  ata ttc gac att gtg  acc aag cag gcc ttt  gac gtc acc      4599
Gly Phe  Ile Phe Asp Ile Val  Thr Lys Gln Ala Phe  Asp Val Thr
    1520                 1525                 1530

atc atg  ttt ctg atc tgc ttg  aat atg gtg acc atg  atg gtg gag      4644
Ile Met  Phe Leu Ile Cys Leu  Asn Met Val Thr Met  Met Val Glu
    1535                 1540                 1545

aca gat  gac caa agt cct gag  aaa atc aac atc ttg  gcc aag atc      4689
Thr Asp  Asp Gln Ser Pro Glu  Lys Ile Asn Ile Leu  Ala Lys Ile
    1550                 1555                 1560

aac ctg  ctc ttt gtg gcc atc  ttc aca ggc gag tgt  att gtc aag      4734
Asn Leu  Leu Phe Val Ala Ile  Phe Thr Gly Glu Cys  Ile Val Lys
    1565                 1570                 1575

ctg gct  gcc ctg cgc cac tac  tac ttc acc aac agc  tgg aat atc      4779
Leu Ala  Ala Leu Arg His Tyr  Tyr Phe Thr Asn Ser  Trp Asn Ile
    1580                 1585                 1590

ttc gac  ttc gtg gtt gtc atc  ctc tcc atc gtg ggc  act gtg ctc      4824
Phe Asp  Phe Val Val Val Ile  Leu Ser Ile Val Gly  Thr Val Leu
    1595                 1600                 1605

tcg gac  atc atc cag aag tac  ttc ttc tcc ccg acg  ctc ttc cga      4869
Ser Asp  Ile Ile Gln Lys Tyr  Phe Phe Ser Pro Thr  Leu Phe Arg
    1610                 1615                 1620

gtc atc  cgc ctg gcc cga ata  ggc cgc atc ctc aga  ctg atc cga      4914
Val Ile  Arg Leu Ala Arg Ile  Gly Arg Ile Leu Arg  Leu Ile Arg
    1625                 1630                 1635

ggg gcc  aag ggg atc cgc acg  ctg ctc ttt gcc ctc  atg atg tcc      4959
Gly Ala  Lys Gly Ile Arg Thr  Leu Leu Phe Ala Leu  Met Met Ser
    1640                 1645                 1650

ctg cct  gcc ctc ttc aac atc  ggg ctg ctg ctc ttc  ctc gtc atg      5004
Leu Pro  Ala Leu Phe Asn Ile  Gly Leu Leu Leu Phe  Leu Val Met
    1655                 1660                 1665

ttc atc  tac tcc atc ttt ggc  atg gcc aac ttc gct  tat gtc aag      5049
Phe Ile  Tyr Ser Ile Phe Gly  Met Ala Asn Phe Ala  Tyr Val Lys
    1670                 1675                 1680

tgg gag  gct ggc atc gac gac  atg ttc aac ttc cag  acc ttc gcc      5094
Trp Glu  Ala Gly Ile Asp Asp  Met Phe Asn Phe Gln  Thr Phe Ala
    1685                 1690                 1695

aac agc  atg ctg tgc ctc ttc  cag atc acc acg tcg  gcc ggc tgg      5139
Asn Ser  Met Leu Cys Leu Phe  Gln Ile Thr Thr Ser  Ala Gly Trp
    1700                 1705                 1710

gat ggc  ctc ctc agc ccc atc  ctc aac act ggg ccg  ccc tac tgc      5184
Asp Gly  Leu Leu Ser Pro Ile  Leu Asn Thr Gly Pro  Pro Tyr Cys
    1715                 1720                 1725

gac ccc  act ctg ccc aac agc  aat ggc tct cgg ggg  gac tgc ggg      5229
Asp Pro  Thr Leu Pro Asn Ser  Asn Gly Ser Arg Gly  Asp Cys Gly
    1730                 1735                 1740

agc cca  gcc gtg ggc atc ctc  ttc ttc acc acc tac  atc atc atc      5274
Ser Pro  Ala Val Gly Ile Leu  Phe Phe Thr Thr Tyr  Ile Ile Ile
    1745                 1750                 1755

tcc ttc  ctc atc gtg gtc aac  atg tac att gcc atc  atc ctg gag      5319
Ser Phe  Leu Ile Val Val Asn  Met Tyr Ile Ala Ile  Ile Leu Glu
    1760                 1765                 1770

aac ttc  agc gtg gcc acg gag  gag agc acc gag ccc  ctg agt gag      5364
Asn Phe  Ser Val Ala Thr Glu  Glu Ser Thr Glu Pro  Leu Ser Glu
    1775                 1780                 1785
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gac gac  ttc gat atg ttc tat  gag atc tgg gag aaa  ttt gac cca      5409
Asp Asp  Phe Asp Met Phe Tyr  Glu Ile Trp Glu Lys  Phe Asp Pro
    1790                 1795                 1800

gag gcc  act cag ttt att gag  tat tcg gtc ctg tct  gac ttt gcc      5454
Glu Ala  Thr Gln Phe Ile Glu  Tyr Ser Val Leu Ser  Asp Phe Ala
    1805                 1810                 1815

gat gcc  ctg tct gag cca ctc  cgt atc gcc aag ccc  aac cag ata      5499
Asp Ala  Leu Ser Glu Pro Leu  Arg Ile Ala Lys Pro  Asn Gln Ile
    1820                 1825                 1830

agc ctc  atc aac atg gac ctg  ccc atg gtg agt ggg  gac cgc atc      5544
Ser Leu  Ile Asn Met Asp Leu  Pro Met Val Ser Gly  Asp Arg Ile
    1835                 1840                 1845

cat tgc  atg gac att ctc ttt  gcc ttc acc aaa agg  gtc ctg ggg      5589
His Cys  Met Asp Ile Leu Phe  Ala Phe Thr Lys Arg  Val Leu Gly
    1850                 1855                 1860

gag tct  ggg gag atg gac gcc  ctg aag atc cag atg  gag gag aag      5634
Glu Ser  Gly Glu Met Asp Ala  Leu Lys Ile Gln Met  Glu Glu Lys
    1865                 1870                 1875

ttc atg  gca gcc aac cca tcc  aag atc tcc tac gag  ccc atc acc      5679
Phe Met  Ala Ala Asn Pro Ser  Lys Ile Ser Tyr Glu  Pro Ile Thr
    1880                 1885                 1890

acc aca  ctc cgg cgc aag cac  gaa gag gtg tcg gcc  atg gtt atc      5724
Thr Thr  Leu Arg Arg Lys His  Glu Glu Val Ser Ala  Met Val Ile
    1895                 1900                 1905

cag aga  gcc ttc cgc agg cac  ctg ctg caa cgc tct  ttg aag cat      5769
Gln Arg  Ala Phe Arg Arg His  Leu Leu Gln Arg Ser  Leu Lys His
    1910                 1915                 1920

gcc tcc  ttc ctc ttc cgt cag  cag gcg ggc agc ggc  ctc tcc gaa      5814
Ala Ser  Phe Leu Phe Arg Gln  Gln Ala Gly Ser Gly  Leu Ser Glu
    1925                 1930                 1935

gag gat  gcc cct gag cga gag  ggc ctc atc gcc tac  gtg atg agt      5859
Glu Asp  Ala Pro Glu Arg Glu  Gly Leu Ile Ala Tyr  Val Met Ser
    1940                 1945                 1950

gag aac  ttc tcc cga ccc ctt  ggc cca ccc tcc agc  tcc tcc atc      5904
Glu Asn  Phe Ser Arg Pro Leu  Gly Pro Pro Ser Ser  Ser Ser Ile
    1955                 1960                 1965

tcc tcc  act tcc ttc cca ccc  tcc tat gac agt gtc  act aga gcc      5949
Ser Ser  Thr Ser Phe Pro Pro  Ser Tyr Asp Ser Val  Thr Arg Ala
    1970                 1975                 1980

acc agc  gat aac ctc cag gtg  cgg ggg tct gac tac  agc cac agt      5994
Thr Ser  Asp Asn Leu Gln Val  Arg Gly Ser Asp Tyr  Ser His Ser
    1985                 1990                 1995

gaa gat  ctc gcc gac ttc ccc  cct tct ccg gac agg  gac cgt gag      6039
Glu Asp  Leu Ala Asp Phe Pro  Pro Ser Pro Asp Arg  Asp Arg Glu
    2000                 2005                 2010

tcc atc  gtg tgagcctcgg cctggctggc caggacacac tgaaaagcag           6088
Ser Ile  Val
    2015

ccttttttcac catggcaaac ctaaatgcag tcagtcamaa accagcctgg ggccttcctg   6148

gctttgggag taagaaatgg gcct                                         6172


<210> SEQ ID NO 2
<211> LENGTH: 2016
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Ala Asn Phe Leu Leu Pro Arg Gly Thr Ser Ser Phe Arg Arg Phe
1               5                  10                  15
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Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln
            20                  25                  30

Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
        35                  40                  45

Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
    50                  55                  60

Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
            100                 105                 110

Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140

Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285

Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320

Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430
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Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His His Thr Ser
545                 550                 555                 560

Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
                565                 570                 575

Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605

Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670

Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
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    850                 855                 860

Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895

Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
945                 950                 955                 960

Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990

Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                 1000                1005

Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

Thr Glu  Glu Glu Ser Ser Lys  Gln Gln Glu Ser Gln  Pro Val Ser
    1070                1075                1080

Gly Gly  Pro Glu Ala Pro Pro  Asp Ser Arg Thr Trp  Ser Gln Val
    1085                1090                1095

Ser Ala  Thr Ala Ser Ser Glu  Ala Glu Ala Ser Ala  Ser Gln Ala
    1100                1105                1110

Asp Trp  Arg Gln Gln Trp Lys  Ala Glu Pro Gln Ala  Pro Gly Cys
    1115                1120                1125

Gly Glu  Thr Pro Glu Asp Ser  Cys Ser Glu Gly Ser  Thr Ala Asp
    1130                1135                1140

Met Thr  Asn Thr Ala Glu Leu  Leu Glu Gln Ile Pro  Asp Leu Gly
    1145                1150                1155

Gln Asp  Val Lys Asp Pro Glu  Asp Cys Phe Thr Glu  Gly Cys Val
    1160                1165                1170

Arg Arg  Cys Pro Cys Cys Ala  Val Asp Thr Thr Gln  Ala Pro Gly
    1175                1180                1185

Lys Val  Trp Trp Arg Leu Arg  Lys Thr Cys Tyr His  Ile Val Glu
    1190                1195                1200

His Ser  Trp Phe Glu Thr Phe  Ile Ile Phe Met Ile  Leu Leu Ser
    1205                1210                1215

Ser Gly  Ala Leu Ala Phe Glu  Asp Ile Tyr Leu Glu  Glu Arg Lys
    1220                1225                1230

Thr Ile  Lys Val Leu Leu Glu  Tyr Ala Asp Lys Met  Phe Thr Tyr
    1235                1240                1245

Val Phe  Val Leu Glu Met Leu  Leu Lys Trp Val Ala  Tyr Gly Phe
    1250                1255                1260
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Lys Lys  Tyr Phe Thr Asn Ala  Trp Cys Trp Leu Asp  Phe Leu Ile
    1265                1270                1275

Val Asp  Val Ser Leu Val Ser  Leu Val Ala Asn Thr  Leu Gly Phe
    1280                1285                1290

Ala Glu  Met Gly Pro Ile Lys  Ser Leu Arg Thr Leu  Arg Ala Leu
    1295                1300                1305

Arg Pro  Leu Arg Ala Leu Ser  Arg Phe Glu Gly Met  Arg Val Val
    1310                1315                1320

Val Asn  Ala Leu Val Gly Ala  Ile Pro Ser Ile Met  Asn Val Leu
    1325                1330                1335

Leu Val  Cys Leu Ile Phe Trp  Leu Ile Phe Ser Ile  Met Gly Val
    1340                1345                1350

Asn Leu  Phe Ala Gly Lys Phe  Gly Arg Cys Ile Asn  Gln Thr Glu
    1355                1360                1365

Gly Asp  Leu Pro Leu Asn Tyr  Thr Ile Val Asn Asn  Lys Ser Gln
    1370                1375                1380

Cys Glu  Ser Leu Asn Leu Thr  Gly Glu Leu Tyr Trp  Thr Lys Val
    1385                1390                1395

Lys Val  Asn Phe Asp Asn Val  Gly Ala Gly Tyr Leu  Ala Leu Leu
    1400                1405                1410

Gln Val  Ala Thr Phe Lys Gly  Trp Met Asp Ile Met  Tyr Ala Ala
    1415                1420                1425

Val Asp  Ser Arg Gly Tyr Glu  Glu Gln Pro Gln Trp  Glu Tyr Asn
    1430                1435                1440

Leu Tyr  Met Tyr Ile Tyr Phe  Val Ile Phe Ile Ile  Phe Gly Ser
    1445                1450                1455

Phe Phe  Thr Leu Asn Leu Phe  Ile Gly Val Ile Ile  Asp Asn Phe
    1460                1465                1470

Asn Gln  Gln Lys Lys Lys Leu  Gly Gly Gln Asp Ile  Phe Met Thr
    1475                1480                1485

Glu Glu  Gln Lys Lys Tyr Tyr  Asn Ala Met Lys Lys  Leu Gly Ser
    1490                1495                1500

Lys Lys  Pro Gln Lys Pro Ile  Pro Arg Pro Leu Asn  Lys Tyr Gln
    1505                1510                1515

Gly Phe  Ile Phe Asp Ile Val  Thr Lys Gln Ala Phe  Asp Val Thr
    1520                1525                1530

Ile Met  Phe Leu Ile Cys Leu  Asn Met Val Thr Met  Met Val Glu
    1535                1540                1545

Thr Asp  Asp Gln Ser Pro Glu  Lys Ile Asn Ile Leu  Ala Lys Ile
    1550                1555                1560

Asn Leu  Leu Phe Val Ala Ile  Phe Thr Gly Glu Cys  Ile Val Lys
    1565                1570                1575

Leu Ala  Ala Leu Arg His Tyr  Tyr Phe Thr Asn Ser  Trp Asn Ile
    1580                1585                1590

Phe Asp  Phe Val Val Val Ile  Leu Ser Ile Val Gly  Thr Val Leu
    1595                1600                1605

Ser Asp  Ile Ile Gln Lys Tyr  Phe Phe Ser Pro Thr  Leu Phe Arg
    1610                1615                1620

Val Ile  Arg Leu Ala Arg Ile  Gly Arg Ile Leu Arg  Leu Ile Arg
    1625                1630                1635

Gly Ala  Lys Gly Ile Arg Thr  Leu Leu Phe Ala Leu  Met Met Ser
    1640                1645                1650
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Leu Pro  Ala Leu Phe Asn Ile  Gly Leu Leu Leu Phe  Leu Val Met
    1655                1660                1665

Phe Ile  Tyr Ser Ile Phe Gly  Met Ala Asn Phe Ala  Tyr Val Lys
    1670                1675                1680

Trp Glu  Ala Gly Ile Asp Asp  Met Phe Asn Phe Gln  Thr Phe Ala
    1685                1690                1695

Asn Ser  Met Leu Cys Leu Phe  Gln Ile Thr Thr Ser  Ala Gly Trp
    1700                1705                1710

Asp Gly  Leu Leu Ser Pro Ile  Leu Asn Thr Gly Pro  Pro Tyr Cys
    1715                1720                1725

Asp Pro  Thr Leu Pro Asn Ser  Asn Gly Ser Arg Gly  Asp Cys Gly
    1730                1735                1740

Ser Pro  Ala Val Gly Ile Leu  Phe Phe Thr Thr Tyr  Ile Ile Ile
    1745                1750                1755

Ser Phe  Leu Ile Val Val Asn  Met Tyr Ile Ala Ile  Ile Leu Glu
    1760                1765                1770

Asn Phe  Ser Val Ala Thr Glu  Glu Ser Thr Glu Pro  Leu Ser Glu
    1775                1780                1785

Asp Asp  Phe Asp Met Phe Tyr  Glu Ile Trp Glu Lys  Phe Asp Pro
    1790                1795                1800

Glu Ala  Thr Gln Phe Ile Glu  Tyr Ser Val Leu Ser  Asp Phe Ala
    1805                1810                1815

Asp Ala  Leu Ser Glu Pro Leu  Arg Ile Ala Lys Pro  Asn Gln Ile
    1820                1825                1830

Ser Leu  Ile Asn Met Asp Leu  Pro Met Val Ser Gly  Asp Arg Ile
    1835                1840                1845

His Cys  Met Asp Ile Leu Phe  Ala Phe Thr Lys Arg  Val Leu Gly
    1850                1855                1860

Glu Ser  Gly Glu Met Asp Ala  Leu Lys Ile Gln Met  Glu Glu Lys
    1865                1870                1875

Phe Met  Ala Ala Asn Pro Ser  Lys Ile Ser Tyr Glu  Pro Ile Thr
    1880                1885                1890

Thr Thr  Leu Arg Arg Lys His  Glu Glu Val Ser Ala  Met Val Ile
    1895                1900                1905

Gln Arg  Ala Phe Arg Arg His  Leu Leu Gln Arg Ser  Leu Lys His
    1910                1915                1920

Ala Ser  Phe Leu Phe Arg Gln  Gln Ala Gly Ser Gly  Leu Ser Glu
    1925                1930                1935

Glu Asp  Ala Pro Glu Arg Glu  Gly Leu Ile Ala Tyr  Val Met Ser
    1940                1945                1950

Glu Asn  Phe Ser Arg Pro Leu  Gly Pro Pro Ser Ser  Ser Ser Ile
    1955                1960                1965

Ser Ser  Thr Ser Phe Pro Pro  Ser Tyr Asp Ser Val  Thr Arg Ala
    1970                1975                1980

Thr Ser  Asp Asn Leu Gln Val  Arg Gly Ser Asp Tyr  Ser His Ser
    1985                1990                1995

Glu Asp  Leu Ala Asp Phe Pro  Pro Ser Pro Asp Arg  Asp Arg Glu
    2000                2005                2010

Ser Ile  Val
    2015
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<221> NAME/KEY: CDS
<222> LOCATION: (1)..(6048)

<400> SEQUENCE: 3

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

aca cgg gag tcc ctg gca gcc atc gag aag cgc atg gcg gag aag caa       96
Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln
            20                  25                  30

gcc cgc ggc tca acc acc ttg cag gag agc cga gag ggg ctg ccc gag      144
Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
        35                  40                  45

gag gag gct ccc cgg ccc cag ctg gac ctg cag gcc tcc aaa aag ctg      192
Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
    50                  55                  60

cca gat ctc tat ggc aat cca ccc caa gag ctc atc gga gag ccc ctg      240
Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

gag gac ctg gac ccc ttc tat agc acc caa aag act ttc atc gta ctg      288
Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

aat aaa ggc aag acc atc ttc cgg ttc agt gcc acc aac gcc ttg tat      336
Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
            100                 105                 110

gtc ctc agt ccc ttc cac ccc atc cgg aga gcg gct gtg aag att ctg      384
Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

gtt cac tcg ctc ttc aac atg ctc atc atg tgc acc atc ctc acc aac      432
Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140

tgc gtg ttc atg gcc cag cac gac cct cca ccc tgg acc aag tat gtc      480
Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

gag tac acc ttc acc gcc att tac acc ttt gag tct ctg gtc aag att      528
Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

ctg gct cga ggc ttc tgc ctg cac gcg ttc act ttc ctt cgg gac cca      576
Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

tgg aac tgg ctg gac ttt agt gtg att atc atg gca tac aca act gaa      624
Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

ttt gtg gac ctg ggc aat gtc tca gcc tta cgc acc ttc cga gtc ctc      672
Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

cgg gcc ctg aaa act ata tca gtc att tca ggg ctg aag acc atc gtg      720
Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

ggg gcc ctg atc cag tct gtg aag aag ctg gct gat gtg atg gtc ctc      768
Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

aca gtc ttc tgc ctc agc gtc ttt gcc ctc atc ggc ctg cag ctc ttc      816
Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

atg ggc aac cta agg cac aag tgc gtg cgc aac ttc aca gcg ctc aac      864
Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285
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ggc acc aac ggc tcc gtg gag gcc gac ggc ttg gtc tgg gaa tcc ctg      912
Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

gac ctt tac ctc agt gat cca gaa aat tac ctg ctc aag aac ggc acc      960
Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320

tct gat gtg tta ctg tgt ggg aac agc tct gac gct ggg aca tgt ccg     1008
Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

gag ggc tac cgg tgc cta aag gca ggc gag aac ccc gac cac ggc tac     1056
Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

acc agc ttc gat tcc ttt gcc tgg gcc ttt ctt gca ctc ttc cgc ctg     1104
Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

atg acg cag gac tgc tgg gag cgc ctc tat cag cag acc ctc agg tcc     1152
Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

gca ggg aag atc tac atg atc ttc ttc atg ctt gtc atc ttc ctg ggg     1200
Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

tcc ttc tac ctg gtg aac ctg atc ctg gcc gtg gtc gca atg gcc tat     1248
Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

gag gag caa aac caa gcc acc atc gct gag acc gag gag aag gaa aag     1296
Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

cgc ttc cag gag gcc atg gaa atg ctc aag aaa gaa cac gag gcc ctc     1344
Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

acc atc agg ggt gtg gat acc gtg tcc cgt agc tcc ttg gag atg tcc     1392
Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

cct ttg gcc cca gta aac agc cat gag aga aga agc aag agg aga aaa     1440
Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

cgg atg tct tca gga act gag gag tgt ggg gag gac agg ctc ccc aag     1488
Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

tct gac tca gaa gat ggt ccc aga gca atg aat cat ctc agc ctc acc     1536
Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

cgt ggc ctc agc agg act tct atg aag cca cgt tcc agc cgc ggg agc     1584
Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

att ttc acc ttt cgc agg cga gac ctg ggt tct gaa gca gat ttt gca     1632
Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

gat gat gaa aac agc aca gcg ggg gag agc gag agc cac cgc aca tca     1680
Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His Arg Thr Ser
545                 550                 555                 560

ctg ctg gtg ccc tgg ccc ctg cgc cgg acc agt gcc cag gga cag ccc     1728
Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
                565                 570                 575

agt ccc gga acc tcg gct cct ggc cac gcc ctc cat ggc aaa aag aac     1776
Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

agc act gtg gac tgc aat ggg gtg gtc tca tta ctg ggg gca ggc gac     1824
Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605
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cca gag gcc aca tcc cca gga agc cac ctc ctc cgc cct gtg atg cta     1872
Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

gag cac ccg cca gac acg acc acg cca tcg gag gag cca ggc ggg ccc     1920
Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

cag atg ctg acc tcc cag gct ccg tgt gta gat ggc ttc gag gag cca     1968
Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

gga gca cgg cag cgg gcc ctc agc gca gtc agc gtc ctc acc agc gca     2016
Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670

ctg gaa gag tta gag gag tct cgc cac aag tgt cca cca tgc tgg aac     2064
Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

cgt ctc gcc cag cgc tac ctg atc tgg gag tgc tgc ccg ctg tgg atg     2112
Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

tcc atc aag cag gga gtg aag ttg gtg gtc atg gac ccg ttt act gac     2160
Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

ctc acc atc act atg tgc atc gta ctc aac aca ctc ttc atg gcg ctg     2208
Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

gag cac tac aac atg aca agt gaa ttc gag gag atg ctg cag gtc gga     2256
Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

aac ctg gtc ttc aca ggg att ttc aca gca gag atg acc ttc aag atc     2304
Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

att gcc ctc gac ccc tac tac tac ttc caa cag ggc tgg aac atc ttc     2352
Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

gac agc atc atc gtc atc ctt agc ctc atg gag ctg ggc ctg tcc cgc     2400
Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

atg agc aac ttg tcg gtg ctg cgc tcc ttc cgc ctg ctg cgg gtc ttc     2448
Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

aag ctg gcc aaa tca tgg ccc acc ctg aac aca ctc atc aag atc atc     2496
Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

ggg aac tca gtg ggg gca ctg ggg aac ctg aca ctg gtg cta gcc atc     2544
Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

atc gtg ttc atc ttt gct gtg gtg ggc atg cag ctc ttt ggc aag aac     2592
Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
    850                 855                 860

tac tcg gag ctg agg gac agc gac tca ggc ctg ctg cct cgc tgg cac     2640
Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

atg atg gac ttc ttt cat gcc ttc ctc atc atc ttc cgc atc ctc tgt     2688
Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895

gga gag tgg atc gag acc atg tgg gac tgc atg gag gtg tcg ggg cag     2736
Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

tca tta tgc ctg ctg gtc ttc ttg ctt gtt atg gtc att ggc aac ctt     2784
Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
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        915                 920                 925

gtg gtc ctg aat ctc ttc ctg gcc ttg ctg ctc agc tcc ttc agt gca     2832
Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

gac aac ctc aca gcc cct gat gag gac aga gag atg aac aac ctc cag     2880
Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
945                 950                 955                 960

ctg gcc ctg gcc cgc atc cag agg ggc ctg cgc ttt gtc aag cgg acc     2928
Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

acc tgg gat ttc tgc tgt ggt ctc ctg cgg cag cgg cct cag aag ccc     2976
Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990

gca gcc ctt gcc gcc cag ggc cag  ctg ccc agc tgc att  gcc acc ccc   3024
Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                 1000                1005

tac tcc  ccg cca ccc cca gag  acg gag aag gtg cct  ccc acc cgc      3069
Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

aag gaa  aca cgg ttt gag gaa  ggc gag caa cca ggc  cag ggc acc      3114
Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

ccc ggg  gat cca gag ccc gtg  tgt gtg ccc atc gct  gtg gcc gag      3159
Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

tca gac  aca gat gac caa gaa  gaa gat gag gag aac  agc ctg ggc      3204
Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

acg gag  gag gag tcc agc aag  cag cag gaa tcc cag  cct gtg tcc      3249
Thr Glu  Glu Glu Ser Ser Lys  Gln Gln Glu Ser Gln  Pro Val Ser
    1070                1075                1080

ggt ggc  cca gag gcc cct ccg  gat tcc agg acc tgg  agc cag gtg      3294
Gly Gly  Pro Glu Ala Pro Pro  Asp Ser Arg Thr Trp  Ser Gln Val
    1085                1090                1095

tca gcg  act gcc tcc tct gag  gcc gag gcc agt gca  tct cag gcc      3339
Ser Ala  Thr Ala Ser Ser Glu  Ala Glu Ala Ser Ala  Ser Gln Ala
    1100                1105                1110

gac tgg  cgg cag cag tgg aaa  gcg gaa ccc cag gcc  cca ggg tgc      3384
Asp Trp  Arg Gln Gln Trp Lys  Ala Glu Pro Gln Ala  Pro Gly Cys
    1115                1120                1125

ggt gag  acc cca gag gac agt  tgc tcc gag ggc agc  aca gca gac      3429
Gly Glu  Thr Pro Glu Asp Ser  Cys Ser Glu Gly Ser  Thr Ala Asp
    1130                1135                1140

atg acc  aac acc gct gag ctc  ctg gag cag atc cct  gac ctc ggc      3474
Met Thr  Asn Thr Ala Glu Leu  Leu Glu Gln Ile Pro  Asp Leu Gly
    1145                1150                1155

cag gat  gtc aag gac cca gag  gac tgc ttc act gaa  ggc tgt gtc      3519
Gln Asp  Val Lys Asp Pro Glu  Asp Cys Phe Thr Glu  Gly Cys Val
    1160                1165                1170

cgg cgc  tgt ccc tgc tgt gcg  gtg gac acc aca cag  gcc cca ggg      3564
Arg Arg  Cys Pro Cys Cys Ala  Val Asp Thr Thr Gln  Ala Pro Gly
    1175                1180                1185

aag gtc  tgg tgg cgg ttg cgc  aag acc tgc tac cac  atc gtg gag      3609
Lys Val  Trp Trp Arg Leu Arg  Lys Thr Cys Tyr His  Ile Val Glu
    1190                1195                1200

cac agc  tgg ttc gag aca ttc  atc atc ttc atg atc  cta ctc agc      3654
His Ser  Trp Phe Glu Thr Phe  Ile Ile Phe Met Ile  Leu Leu Ser
    1205                1210                1215

agt gga  gcg ctg gcc ttc gag  gac atc tac cta gag  gag cgg aag      3699
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Ser Gly  Ala Leu Ala Phe Glu  Asp Ile Tyr Leu Glu  Glu Arg Lys
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acc atc  aag gtt ctg ctt gag  tat gcc gac aag atg  ttc aca tat      3744
Thr Ile  Lys Val Leu Leu Glu  Tyr Ala Asp Lys Met  Phe Thr Tyr
    1235                1240                1245

gtc ttc  gtg ctg gag atg ctg  ctc aag tgg gtg gcc  tac ggc ttc      3789
Val Phe  Val Leu Glu Met Leu  Leu Lys Trp Val Ala  Tyr Gly Phe
    1250                1255                1260

aag aag  tac ttc acc aat gcc  tgg tgc tgg ctc gac  ttc ctc atc      3834
Lys Lys  Tyr Phe Thr Asn Ala  Trp Cys Trp Leu Asp  Phe Leu Ile
    1265                1270                1275

gta gac  gtc tct ctg gtc agc  ctg gtg gcc aac acc  ctg ggc ttt      3879
Val Asp  Val Ser Leu Val Ser  Leu Val Ala Asn Thr  Leu Gly Phe
    1280                1285                1290

gcc gag  atg ggt ccc atc aag  tca ctg cgg acg ctg  cgt gca ctc      3924
Ala Glu  Met Gly Pro Ile Lys  Ser Leu Arg Thr Leu  Arg Ala Leu
    1295                1300                1305

cgt cct  ctg aga gct ctg tca  cga ttt gag ggc atg  agg gtg gtg      3969
Arg Pro  Leu Arg Ala Leu Ser  Arg Phe Glu Gly Met  Arg Val Val
    1310                1315                1320

gtc aat  gcc ctg gtg ggc gcc  atc ccg tcc atc atg  aac gtc ctc      4014
Val Asn  Ala Leu Val Gly Ala  Ile Pro Ser Ile Met  Asn Val Leu
    1325                1330                1335

ctc gtc  tgc ctc atc ttc tgg  ctc atc ttc agc atc  atg ggc gtg      4059
Leu Val  Cys Leu Ile Phe Trp  Leu Ile Phe Ser Ile  Met Gly Val
    1340                1345                1350

aac ctc  ttt gcg ggg aag ttt  ggg agg tgc atc aac  cag aca gag      4104
Asn Leu  Phe Ala Gly Lys Phe  Gly Arg Cys Ile Asn  Gln Thr Glu
    1355                1360                1365

gga gac  ttg cct ttg aac tac  acc atc gtg aac aac  aag agc cag      4149
Gly Asp  Leu Pro Leu Asn Tyr  Thr Ile Val Asn Asn  Lys Ser Gln
    1370                1375                1380

tgt gag  tcc ttg aac ttg acc  gga gaa ttg tac tgg  acc aag gtg      4194
Cys Glu  Ser Leu Asn Leu Thr  Gly Glu Leu Tyr Trp  Thr Lys Val
    1385                1390                1395

aaa gtc  aac ttt gac aac gtg  ggg gcc ggg tac ctg  gcc ctt ctg      4239
Lys Val  Asn Phe Asp Asn Val  Gly Ala Gly Tyr Leu  Ala Leu Leu
    1400                1405                1410

cag gtg  gca aca ttt aaa ggc  tgg atg gac att atg  tat gca gct      4284
Gln Val  Ala Thr Phe Lys Gly  Trp Met Asp Ile Met  Tyr Ala Ala
    1415                1420                1425

gtg gac  tcc agg ggg tat gaa  gag cag cct cag tgg  gaa tac aac      4329
Val Asp  Ser Arg Gly Tyr Glu  Glu Gln Pro Gln Trp  Glu Tyr Asn
    1430                1435                1440

ctc tac  atg tac atc tat ttt  gtc att ttc atc atc  ttt ggg tct      4374
Leu Tyr  Met Tyr Ile Tyr Phe  Val Ile Phe Ile Ile  Phe Gly Ser
    1445                1450                1455

ttc ttc  acc ctg aac ctc ttt  att ggt gtc atc att  gac aac ttc      4419
Phe Phe  Thr Leu Asn Leu Phe  Ile Gly Val Ile Ile  Asp Asn Phe
    1460                1465                1470

aac caa  cag aag aaa aag tta  ggg ggc cag gac atc  ttc atg aca      4464
Asn Gln  Gln Lys Lys Lys Leu  Gly Gly Gln Asp Ile  Phe Met Thr
    1475                1480                1485

gag gag  cag aag aag tac tac  aat gcc atg aag aag  ctg ggc tcc      4509
Glu Glu  Gln Lys Lys Tyr Tyr  Asn Ala Met Lys Lys  Leu Gly Ser
    1490                1495                1500

aag aag  ccc cag aag ccc atc  cca cgg ccc ctg aac  aag tac cag      4554
Lys Lys  Pro Gln Lys Pro Ile  Pro Arg Pro Leu Asn  Lys Tyr Gln
    1505                1510                1515
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ggc ttc  ata ttc gac att gtg  acc aag cag gcc ttt  gac gtc acc      4599
Gly Phe  Ile Phe Asp Ile Val  Thr Lys Gln Ala Phe  Asp Val Thr
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atc atg  ttt ctg atc tgc ttg  aat atg gtg acc atg  atg gtg gag      4644
Ile Met  Phe Leu Ile Cys Leu  Asn Met Val Thr Met  Met Val Glu
    1535                 1540                 1545

aca gat  gac caa agt cct gag  aaa atc aac atc ttg  gcc aag atc      4689
Thr Asp  Asp Gln Ser Pro Glu  Lys Ile Asn Ile Leu  Ala Lys Ile
    1550                 1555                 1560

aac ctg  ctc ttt gtg gcc atc  ttc aca ggc gag tgt  att gtc aag      4734
Asn Leu  Leu Phe Val Ala Ile  Phe Thr Gly Glu Cys  Ile Val Lys
    1565                 1570                 1575

ctg gct  gcc ctg cgc cac tac  tac ttc acc aac agc  tgg aat atc      4779
Leu Ala  Ala Leu Arg His Tyr  Tyr Phe Thr Asn Ser  Trp Asn Ile
    1580                 1585                 1590

ttc gac  ttc gtg gtt gtc atc  ctc tcc atc gtg ggc  act gtg ctc      4824
Phe Asp  Phe Val Val Val Ile  Leu Ser Ile Val Gly  Thr Val Leu
    1595                 1600                 1605

tcg gac  atc atc cag aag tac  ttc ttc tcc ccg acg  ctc ttc cga      4869
Ser Asp  Ile Ile Gln Lys Tyr  Phe Phe Ser Pro Thr  Leu Phe Arg
    1610                 1615                 1620

gtc atc  cgc ctg gcc cga ata  ggc cgc atc ctc aga  ctg atc cga      4914
Val Ile  Arg Leu Ala Arg Ile  Gly Arg Ile Leu Arg  Leu Ile Arg
    1625                 1630                 1635

ggg gcc  aag ggg atc cgc acg  ctg ctc ttt gcc ctc  atg atg tcc      4959
Gly Ala  Lys Gly Ile Arg Thr  Leu Leu Phe Ala Leu  Met Met Ser
    1640                 1645                 1650

ctg cct  gcc ctc ttc aac atc  ggg ctg ctg ctc ttc  ctc gtc atg      5004
Leu Pro  Ala Leu Phe Asn Ile  Gly Leu Leu Leu Phe  Leu Val Met
    1655                 1660                 1665

ttc atc  tac tcc atc ttt ggc  atg gcc aac ttc gct  tat gtc aag      5049
Phe Ile  Tyr Ser Ile Phe Gly  Met Ala Asn Phe Ala  Tyr Val Lys
    1670                 1675                 1680

tgg gag  gct ggc atc gac gac  atg ttc aac ttc cag  acc ttc gcc      5094
Trp Glu  Ala Gly Ile Asp Asp  Met Phe Asn Phe Gln  Thr Phe Ala
    1685                 1690                 1695

aac agc  atg ctg tgc ctc ttc  cag atc acc acg tcg  gcc ggc tgg      5139
Asn Ser  Met Leu Cys Leu Phe  Gln Ile Thr Thr Ser  Ala Gly Trp
    1700                 1705                 1710

gat ggc  ctc ctc agc ccc atc  ctc aac act ggg ccg  ccc tac tgc      5184
Asp Gly  Leu Leu Ser Pro Ile  Leu Asn Thr Gly Pro  Pro Tyr Cys
    1715                 1720                 1725

gac ccc  act ctg ccc aac agc  aat ggc tct cgg ggg  gac tgc ggg      5229
Asp Pro  Thr Leu Pro Asn Ser  Asn Gly Ser Arg Gly  Asp Cys Gly
    1730                 1735                 1740

agc cca  gcc gtg ggc atc ctc  ttc ttc acc acc tac  atc atc atc      5274
Ser Pro  Ala Val Gly Ile Leu  Phe Phe Thr Thr Tyr  Ile Ile Ile
    1745                 1750                 1755

tcc ttc  ctc atc gtg gtc aac  atg tac att gcc atc  atc ctg gag      5319
Ser Phe  Leu Ile Val Val Asn  Met Tyr Ile Ala Ile  Ile Leu Glu
    1760                 1765                 1770

aac ttc  agc gtg gcc acg gag  gag agc acc gag ccc  ctg agt gag      5364
Asn Phe  Ser Val Ala Thr Glu  Glu Ser Thr Glu Pro  Leu Ser Glu
    1775                 1780                 1785

gac gac  ttc gat atg ttc tat  gag atc tgg gag aaa  ttt gac cca      5409
Asp Asp  Phe Asp Met Phe Tyr  Glu Ile Trp Glu Lys  Phe Asp Pro
    1790                 1795                 1800

gag gcc  act cag ttt att gag  tat tcg gtc ctg tct  gac ttt gcc      5454
Glu Ala  Thr Gln Phe Ile Glu  Tyr Ser Val Leu Ser  Asp Phe Ala
    1805                 1810                 1815
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gat gcc  ctg tct gag cca ctc  cgt atc gcc aag ccc  aac cag ata      5499
Asp Ala  Leu Ser Glu Pro Leu  Arg Ile Ala Lys Pro  Asn Gln Ile
    1820                 1825                 1830

agc ctc  atc aac atg gac ctg  ccc atg gtg agt ggg  gac cgc atc      5544
Ser Leu  Ile Asn Met Asp Leu  Pro Met Val Ser Gly  Asp Arg Ile
    1835                 1840                 1845

cat tgc  atg gac att ctc ttt  gcc ttc acc aaa agg  gtc ctg ggg      5589
His Cys  Met Asp Ile Leu Phe  Ala Phe Thr Lys Arg  Val Leu Gly
    1850                 1855                 1860

gag tct  ggg gag atg gac gcc  ctg aag atc cag atg  gag gag aag      5634
Glu Ser  Gly Glu Met Asp Ala  Leu Lys Ile Gln Met  Glu Glu Lys
    1865                 1870                 1875

ttc atg  gca gcc aac cca tcc  aag atc tcc tac gag  ccc atc acc      5679
Phe Met  Ala Ala Asn Pro Ser  Lys Ile Ser Tyr Glu  Pro Ile Thr
    1880                 1885                 1890

acc aca  ctc cgg cgc aag cac  gaa gag gtg tcg gcc  atg gtt atc      5724
Thr Thr  Leu Arg Arg Lys His  Glu Glu Val Ser Ala  Met Val Ile
    1895                 1900                 1905

cag aga  gcc ttc cgc agg cac  ctg ctg caa cgc tct  ttg aag cat      5769
Gln Arg  Ala Phe Arg Arg His  Leu Leu Gln Arg Ser  Leu Lys His
    1910                 1915                 1920

gcc tcc  ttc ctc ttc cgt cag  cag gcg ggc agc ggc  ctc tcc gaa      5814
Ala Ser  Phe Leu Phe Arg Gln  Gln Ala Gly Ser Gly  Leu Ser Glu
    1925                 1930                 1935

gag gat  gcc cct gag cga gag  ggc ctc atc gcc tac  gtg atg agt      5859
Glu Asp  Ala Pro Glu Arg Glu  Gly Leu Ile Ala Tyr  Val Met Ser
    1940                 1945                 1950

gag aac  ttc tcc cga ccc ctt  ggc cca ccc tcc agc  tcc tcc atc      5904
Glu Asn  Phe Ser Arg Pro Leu  Gly Pro Pro Ser Ser  Ser Ser Ile
    1955                 1960                 1965

tcc tcc  act tcc ttc cca ccc  tcc tat gac agt gtc  act aga gcc      5949
Ser Ser  Thr Ser Phe Pro Pro  Ser Tyr Asp Ser Val  Thr Arg Ala
    1970                 1975                 1980

acc agc  gat aac ctc cag gtg  cgg ggg tct gac tac  agc cac agt      5994
Thr Ser  Asp Asn Leu Gln Val  Arg Gly Ser Asp Tyr  Ser His Ser
    1985                 1990                 1995

gaa gat  ctc gcc gac ttc ccc  cct tct ccg gac agg  gac cgt gag      6039
Glu Asp  Leu Ala Asp Phe Pro  Pro Ser Pro Asp Arg  Asp Arg Glu
    2000                 2005                 2010

tcc atc  gtg tgagcctcgg cctggctggc caggacacac tgaaaagcag           6088
Ser Ile  Val
    2015

ccttttttcac catggcaaac ctaaatgcag tcagtcamaa accagcctgg ggccttcctg   6148

gctttgggag taagaaatgg gcct                                         6172


<210> SEQ ID NO 4
<211> LENGTH: 2016
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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

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

Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
        35                  40                  45

Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
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    50                  55                  60

Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
            100                 105                 110

Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140

Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285

Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320

Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480
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Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His Arg Thr Ser
545                 550                 555                 560

Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
                565                 570                 575

Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605

Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670

Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
    850                 855                 860

Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895
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Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
945                 950                 955                 960

Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990

Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                 1000                1005

Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

Thr Glu  Glu Glu Ser Ser Lys  Gln Gln Glu Ser Gln  Pro Val Ser
    1070                1075                1080

Gly Gly  Pro Glu Ala Pro Pro  Asp Ser Arg Thr Trp  Ser Gln Val
    1085                1090                1095

Ser Ala  Thr Ala Ser Ser Glu  Ala Glu Ala Ser Ala  Ser Gln Ala
    1100                1105                1110

Asp Trp  Arg Gln Gln Trp Lys  Ala Glu Pro Gln Ala  Pro Gly Cys
    1115                1120                1125

Gly Glu  Thr Pro Glu Asp Ser  Cys Ser Glu Gly Ser  Thr Ala Asp
    1130                1135                1140

Met Thr  Asn Thr Ala Glu Leu  Leu Glu Gln Ile Pro  Asp Leu Gly
    1145                1150                1155

Gln Asp  Val Lys Asp Pro Glu  Asp Cys Phe Thr Glu  Gly Cys Val
    1160                1165                1170

Arg Arg  Cys Pro Cys Cys Ala  Val Asp Thr Thr Gln  Ala Pro Gly
    1175                1180                1185

Lys Val  Trp Trp Arg Leu Arg  Lys Thr Cys Tyr His  Ile Val Glu
    1190                1195                1200

His Ser  Trp Phe Glu Thr Phe  Ile Ile Phe Met Ile  Leu Leu Ser
    1205                1210                1215

Ser Gly  Ala Leu Ala Phe Glu  Asp Ile Tyr Leu Glu  Glu Arg Lys
    1220                1225                1230

Thr Ile  Lys Val Leu Leu Glu  Tyr Ala Asp Lys Met  Phe Thr Tyr
    1235                1240                1245

Val Phe  Val Leu Glu Met Leu  Leu Lys Trp Val Ala  Tyr Gly Phe
    1250                1255                1260

Lys Lys  Tyr Phe Thr Asn Ala  Trp Cys Trp Leu Asp  Phe Leu Ile
    1265                1270                1275

Val Asp  Val Ser Leu Val Ser  Leu Val Ala Asn Thr  Leu Gly Phe
    1280                1285                1290

Ala Glu  Met Gly Pro Ile Lys  Ser Leu Arg Thr Leu  Arg Ala Leu
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    1295                1300                1305

Arg Pro  Leu Arg Ala Leu Ser  Arg Phe Glu Gly Met  Arg Val Val
    1310                1315                1320

Val Asn  Ala Leu Val Gly Ala  Ile Pro Ser Ile Met  Asn Val Leu
    1325                1330                1335

Leu Val  Cys Leu Ile Phe Trp  Leu Ile Phe Ser Ile  Met Gly Val
    1340                1345                1350

Asn Leu  Phe Ala Gly Lys Phe  Gly Arg Cys Ile Asn  Gln Thr Glu
    1355                1360                1365

Gly Asp  Leu Pro Leu Asn Tyr  Thr Ile Val Asn Asn  Lys Ser Gln
    1370                1375                1380

Cys Glu  Ser Leu Asn Leu Thr  Gly Glu Leu Tyr Trp  Thr Lys Val
    1385                1390                1395

Lys Val  Asn Phe Asp Asn Val  Gly Ala Gly Tyr Leu  Ala Leu Leu
    1400                1405                1410

Gln Val  Ala Thr Phe Lys Gly  Trp Met Asp Ile Met  Tyr Ala Ala
    1415                1420                1425

Val Asp  Ser Arg Gly Tyr Glu  Glu Gln Pro Gln Trp  Glu Tyr Asn
    1430                1435                1440

Leu Tyr  Met Tyr Ile Tyr Phe  Val Ile Phe Ile Ile  Phe Gly Ser
    1445                1450                1455

Phe Phe  Thr Leu Asn Leu Phe  Ile Gly Val Ile Ile  Asp Asn Phe
    1460                1465                1470

Asn Gln  Gln Lys Lys Lys Leu  Gly Gly Gln Asp Ile  Phe Met Thr
    1475                1480                1485

Glu Glu  Gln Lys Lys Tyr Tyr  Asn Ala Met Lys Lys  Leu Gly Ser
    1490                1495                1500

Lys Lys  Pro Gln Lys Pro Ile  Pro Arg Pro Leu Asn  Lys Tyr Gln
    1505                1510                1515

Gly Phe  Ile Phe Asp Ile Val  Thr Lys Gln Ala Phe  Asp Val Thr
    1520                1525                1530

Ile Met  Phe Leu Ile Cys Leu  Asn Met Val Thr Met  Met Val Glu
    1535                1540                1545

Thr Asp  Asp Gln Ser Pro Glu  Lys Ile Asn Ile Leu  Ala Lys Ile
    1550                1555                1560

Asn Leu  Leu Phe Val Ala Ile  Phe Thr Gly Glu Cys  Ile Val Lys
    1565                1570                1575

Leu Ala  Ala Leu Arg His Tyr  Tyr Phe Thr Asn Ser  Trp Asn Ile
    1580                1585                1590

Phe Asp  Phe Val Val Val Ile  Leu Ser Ile Val Gly  Thr Val Leu
    1595                1600                1605

Ser Asp  Ile Ile Gln Lys Tyr  Phe Phe Ser Pro Thr  Leu Phe Arg
    1610                1615                1620

Val Ile  Arg Leu Ala Arg Ile  Gly Arg Ile Leu Arg  Leu Ile Arg
    1625                1630                1635

Gly Ala  Lys Gly Ile Arg Thr  Leu Leu Phe Ala Leu  Met Met Ser
    1640                1645                1650

Leu Pro  Ala Leu Phe Asn Ile  Gly Leu Leu Leu Phe  Leu Val Met
    1655                1660                1665

Phe Ile  Tyr Ser Ile Phe Gly  Met Ala Asn Phe Ala  Tyr Val Lys
    1670                1675                1680

Trp Glu  Ala Gly Ile Asp Asp  Met Phe Asn Phe Gln  Thr Phe Ala
    1685                1690                1695
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Asn Ser  Met Leu Cys Leu Phe  Gln Ile Thr Thr Ser  Ala Gly Trp
    1700                1705                1710

Asp Gly  Leu Leu Ser Pro Ile  Leu Asn Thr Gly Pro  Pro Tyr Cys
    1715                1720                1725

Asp Pro  Thr Leu Pro Asn Ser  Asn Gly Ser Arg Gly  Asp Cys Gly
    1730                1735                1740

Ser Pro  Ala Val Gly Ile Leu  Phe Phe Thr Thr Tyr  Ile Ile Ile
    1745                1750                1755

Ser Phe  Leu Ile Val Val Asn  Met Tyr Ile Ala Ile  Ile Leu Glu
    1760                1765                1770

Asn Phe  Ser Val Ala Thr Glu  Glu Ser Thr Glu Pro  Leu Ser Glu
    1775                1780                1785

Asp Asp  Phe Asp Met Phe Tyr  Glu Ile Trp Glu Lys  Phe Asp Pro
    1790                1795                1800

Glu Ala  Thr Gln Phe Ile Glu  Tyr Ser Val Leu Ser  Asp Phe Ala
    1805                1810                1815

Asp Ala  Leu Ser Glu Pro Leu  Arg Ile Ala Lys Pro  Asn Gln Ile
    1820                1825                1830

Ser Leu  Ile Asn Met Asp Leu  Pro Met Val Ser Gly  Asp Arg Ile
    1835                1840                1845

His Cys  Met Asp Ile Leu Phe  Ala Phe Thr Lys Arg  Val Leu Gly
    1850                1855                1860

Glu Ser  Gly Glu Met Asp Ala  Leu Lys Ile Gln Met  Glu Glu Lys
    1865                1870                1875

Phe Met  Ala Ala Asn Pro Ser  Lys Ile Ser Tyr Glu  Pro Ile Thr
    1880                1885                1890

Thr Thr  Leu Arg Arg Lys His  Glu Glu Val Ser Ala  Met Val Ile
    1895                1900                1905

Gln Arg  Ala Phe Arg Arg His  Leu Leu Gln Arg Ser  Leu Lys His
    1910                1915                1920

Ala Ser  Phe Leu Phe Arg Gln  Gln Ala Gly Ser Gly  Leu Ser Glu
    1925                1930                1935

Glu Asp  Ala Pro Glu Arg Glu  Gly Leu Ile Ala Tyr  Val Met Ser
    1940                1945                1950

Glu Asn  Phe Ser Arg Pro Leu  Gly Pro Pro Ser Ser  Ser Ser Ile
    1955                1960                1965

Ser Ser  Thr Ser Phe Pro Pro  Ser Tyr Asp Ser Val  Thr Arg Ala
    1970                1975                1980

Thr Ser  Asp Asn Leu Gln Val  Arg Gly Ser Asp Tyr  Ser His Ser
    1985                1990                1995

Glu Asp  Leu Ala Asp Phe Pro  Pro Ser Pro Asp Arg  Asp Arg Glu
    2000                2005                2010

Ser Ile  Val
    2015
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<210> SEQ ID NO 5
<211> LENGTH: 6169
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(6045)

<400> SEQUENCE: 5

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atg gca aac ttc cta tta cct agg ggc acc agc agc ttc cgc agg ttc       48
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Met Ala Asn Phe Leu Leu Pro Arg Gly Thr Ser Ser Phe Arg Arg Phe
1               5                  10                  15

aca cgg gag tcc ctg gca gcc atc gag aag cgc atg gcg gag aag caa       96
Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln
            20                  25                  30

gcc cgc ggc tca acc acc ttg cag gag agc cga gag ggg ctg ccc gag      144
Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
        35                  40                  45

gag gag gct ccc cgg ccc cag ctg gac ctg cag gcc tcc aaa aag ctg      192
Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
    50                  55                  60

cca gat ctc tat ggc aat cca ccc caa gag ctc atc gga gag ccc ctg      240
Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

gag gac ctg gac ccc ttc tat agc acc caa aag act ttc atc gta ctg      288
Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

aat aaa ggc aag acc atc ttc cgg ttc agt gcc acc aac gcc ttg tat      336
Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
            100                 105                 110

gtc ctc agt ccc ttc cac ccc atc cgg aga gcg gct gtg aag att ctg      384
Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

gtt cac tcg ctc ttc aac atg ctc atc atg tgc acc atc ctc acc aac      432
Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140

tgc gtg ttc atg gcc cag cac gac cct cca ccc tgg acc aag tat gtc      480
Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

gag tac acc ttc acc gcc att tac acc ttt gag tct ctg gtc aag att      528
Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

ctg gct cga ggc ttc tgc ctg cac gcg ttc act ttc ctt cgg gac cca      576
Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

tgg aac tgg ctg gac ttt agt gtg att atc atg gca tac aca act gaa      624
Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

ttt gtg gac ctg ggc aat gtc tca gcc tta cgc acc ttc cga gtc ctc      672
Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

cgg gcc ctg aaa act ata tca gtc att tca ggg ctg aag acc atc gtg      720
Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

ggg gcc ctg atc cag tct gtg aag aag ctg gct gat gtg atg gtc ctc      768
Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

aca gtc ttc tgc ctc agc gtc ttt gcc ctc atc ggc ctg cag ctc ttc      816
Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

atg ggc aac cta agg cac aag tgc gtg cgc aac ttc aca gcg ctc aac      864
Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285

ggc acc aac ggc tcc gtg gag gcc gac ggc ttg gtc tgg gaa tcc ctg      912
Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

gac ctt tac ctc agt gat cca gaa aat tac ctg ctc aag aac ggc acc      960
Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320
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tct gat gtg tta ctg tgt ggg aac agc tct gac gct ggg aca tgt ccg     1008
Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

gag ggc tac cgg tgc cta aag gca ggc gag aac ccc gac cac ggc tac     1056
Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

acc agc ttc gat tcc ttt gcc tgg gcc ttt ctt gca ctc ttc cgc ctg     1104
Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

atg acg cag gac tgc tgg gag cgc ctc tat cag cag acc ctc agg tcc     1152
Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

gca ggg aag atc tac atg atc ttc ttc atg ctt gtc atc ttc ctg ggg     1200
Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

tcc ttc tac ctg gtg aac ctg atc ctg gcc gtg gtc gca atg gcc tat     1248
Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

gag gag caa aac caa gcc acc atc gct gag acc gag gag aag gaa aag     1296
Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

cgc ttc cag gag gcc atg gaa atg ctc aag aaa gaa cac gag gcc ctc     1344
Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

acc atc agg ggt gtg gat acc gtg tcc cgt agc tcc ttg gag atg tcc     1392
Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

cct ttg gcc cca gta aac agc cat gag aga aga agc aag agg aga aaa     1440
Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

cgg atg tct tca gga act gag gag tgt ggg gag gac agg ctc ccc aag     1488
Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

tct gac tca gaa gat ggt ccc aga gca atg aat cat ctc agc ctc acc     1536
Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

cgt ggc ctc agc agg act tct atg aag cca cgt tcc agc cgc ggg agc     1584
Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

att ttc acc ttt cgc agg cga gac ctg ggt tct gaa gca gat ttt gca     1632
Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

gat gat gaa aac agc aca gcg ggg gag agc gag agc cac cac aca tca     1680
Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His His Thr Ser
545                 550                 555                 560

ctg ctg gtg ccc tgg ccc ctg cgc cgg acc agt gcc cag gga cag ccc     1728
Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
                565                 570                 575

agt ccc gga acc tcg gct cct ggc cac gcc ctc cat ggc aaa aag aac     1776
Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

agc act gtg gac tgc aat ggg gtg gtc tca tta ctg ggg gca ggc gac     1824
Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605

cca gag gcc aca tcc cca gga agc cac ctc ctc cgc cct gtg atg cta     1872
Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

gag cac ccg cca gac acg acc acg cca tcg gag gag cca ggc ggg ccc     1920
Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640
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cag atg ctg acc tcc cag gct ccg tgt gta gat ggc ttc gag gag cca     1968
Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

gga gca cgg cag cgg gcc ctc agc gca gtc agc gtc ctc acc agc gca     2016
Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670

ctg gaa gag tta gag gag tct cgc cac aag tgt cca cca tgc tgg aac     2064
Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

cgt ctc gcc cag cgc tac ctg atc tgg gag tgc tgc ccg ctg tgg atg     2112
Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

tcc atc aag cag gga gtg aag ttg gtg gtc atg gac ccg ttt act gac     2160
Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

ctc acc atc act atg tgc atc gta ctc aac aca ctc ttc atg gcg ctg     2208
Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

gag cac tac aac atg aca agt gaa ttc gag gag atg ctg cag gtc gga     2256
Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

aac ctg gtc ttc aca ggg att ttc aca gca gag atg acc ttc aag atc     2304
Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

att gcc ctc gac ccc tac tac tac ttc caa cag ggc tgg aac atc ttc     2352
Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

gac agc atc atc gtc atc ctt agc ctc atg gag ctg ggc ctg tcc cgc     2400
Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

atg agc aac ttg tcg gtg ctg cgc tcc ttc cgc ctg ctg cgg gtc ttc     2448
Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

aag ctg gcc aaa tca tgg ccc acc ctg aac aca ctc atc aag atc atc     2496
Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

ggg aac tca gtg ggg gca ctg ggg aac ctg aca ctg gtg cta gcc atc     2544
Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

atc gtg ttc atc ttt gct gtg gtg ggc atg cag ctc ttt ggc aag aac     2592
Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
    850                 855                 860

tac tcg gag ctg agg gac agc gac tca ggc ctg ctg cct cgc tgg cac     2640
Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

atg atg gac ttc ttt cat gcc ttc ctc atc atc ttc cgc atc ctc tgt     2688
Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895

gga gag tgg atc gag acc atg tgg gac tgc atg gag gtg tcg ggg cag     2736
Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

tca tta tgc ctg ctg gtc ttc ttg ctt gtt atg gtc att ggc aac ctt     2784
Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

gtg gtc ctg aat ctc ttc ctg gcc ttg ctg ctc agc tcc ttc agt gca     2832
Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

gac aac ctc aca gcc cct gat gag gac aga gag atg aac aac ctc cag     2880
Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
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945                 950                 955                 960

ctg gcc ctg gcc cgc atc cag agg ggc ctg cgc ttt gtc aag cgg acc     2928
Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

acc tgg gat ttc tgc tgt ggt ctc ctg cgg cag cgg cct cag aag ccc     2976
Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990

gca gcc ctt gcc gcc cag ggc cag  ctg ccc agc tgc att  gcc acc ccc   3024
Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                 1000                1005

tac tcc  ccg cca ccc cca gag  acg gag aag gtg cct  ccc acc cgc      3069
Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

aag gaa  aca cgg ttt gag gaa  ggc gag caa cca ggc  cag ggc acc      3114
Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

ccc ggg  gat cca gag ccc gtg  tgt gtg ccc atc gct  gtg gcc gag      3159
Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

tca gac  aca gat gac caa gaa  gaa gat gag gag aac  agc ctg ggc      3204
Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

acg gag  gag gag tcc agc aag  cag gaa tcc cag cct  gtg tcc ggt      3249
Thr Glu  Glu Glu Ser Ser Lys  Gln Glu Ser Gln Pro  Val Ser Gly
    1070                1075                1080

ggc cca  gag gcc cct ccg gat  tcc agg acc tgg agc  cag gtg tca      3294
Gly Pro  Glu Ala Pro Pro Asp  Ser Arg Thr Trp Ser  Gln Val Ser
    1085                1090                1095

gcg act  gcc tcc tct gag gcc  gag gcc agt gca tct  cag gcc gac      3339
Ala Thr  Ala Ser Ser Glu Ala  Glu Ala Ser Ala Ser  Gln Ala Asp
    1100                1105                1110

tgg cgg  cag cag tgg aaa gcg  gaa ccc cag gcc cca  ggg tgc ggt      3384
Trp Arg  Gln Gln Trp Lys Ala  Glu Pro Gln Ala Pro  Gly Cys Gly
    1115                1120                1125

gag acc  cca gag gac agt tgc  tcc gag ggc agc aca  gca gac atg      3429
Glu Thr  Pro Glu Asp Ser Cys  Ser Glu Gly Ser Thr  Ala Asp Met
    1130                1135                1140

acc aac  acc gct gag ctc ctg  gag cag atc cct gac  ctc ggc cag      3474
Thr Asn  Thr Ala Glu Leu Leu  Glu Gln Ile Pro Asp  Leu Gly Gln
    1145                1150                1155

gat gtc  aag gac cca gag gac  tgc ttc act gaa ggc  tgt gtc cgg      3519
Asp Val  Lys Asp Pro Glu Asp  Cys Phe Thr Glu Gly  Cys Val Arg
    1160                1165                1170

cgc tgt  ccc tgc tgt gcg gtg  gac acc aca cag gcc  cca ggg aag      3564
Arg Cys  Pro Cys Cys Ala Val  Asp Thr Thr Gln Ala  Pro Gly Lys
    1175                1180                1185

gtc tgg  tgg cgg ttg cgc aag  acc tgc tac cac atc  gtg gag cac      3609
Val Trp  Trp Arg Leu Arg Lys  Thr Cys Tyr His Ile  Val Glu His
    1190                1195                1200

agc tgg  ttc gag aca ttc atc  atc ttc atg atc cta  ctc agc agt      3654
Ser Trp  Phe Glu Thr Phe Ile  Ile Phe Met Ile Leu  Leu Ser Ser
    1205                1210                1215

gga gcg  ctg gcc ttc gag gac  atc tac cta gag gag  cgg aag acc      3699
Gly Ala  Leu Ala Phe Glu Asp  Ile Tyr Leu Glu Glu  Arg Lys Thr
    1220                1225                1230

atc aag  gtt ctg ctt gag tat  gcc gac aag atg ttc  aca tat gtc      3744
Ile Lys  Val Leu Leu Glu Tyr  Ala Asp Lys Met Phe  Thr Tyr Val
    1235                1240                1245

ttc gtg  ctg gag atg ctg ctc  aag tgg gtg gcc tac  ggc ttc aag      3789
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Phe Val  Leu Glu Met Leu Leu  Lys Trp Val Ala Tyr  Gly Phe Lys
    1250                1255                1260

aag tac  ttc acc aat gcc tgg  tgc tgg ctc gac ttc  ctc atc gta      3834
Lys Tyr  Phe Thr Asn Ala Trp  Cys Trp Leu Asp Phe  Leu Ile Val
    1265                1270                1275

gac gtc  tct ctg gtc agc ctg  gtg gcc aac acc ctg  ggc ttt gcc      3879
Asp Val  Ser Leu Val Ser Leu  Val Ala Asn Thr Leu  Gly Phe Ala
    1280                1285                1290

gag atg  ggt ccc atc aag tca  ctg cgg acg ctg cgt  gca ctc cgt      3924
Glu Met  Gly Pro Ile Lys Ser  Leu Arg Thr Leu Arg  Ala Leu Arg
    1295                1300                1305

cct ctg  aga gct ctg tca cga  ttt gag ggc atg agg  gtg gtg gtc      3969
Pro Leu  Arg Ala Leu Ser Arg  Phe Glu Gly Met Arg  Val Val Val
    1310                1315                1320

aat gcc  ctg gtg ggc gcc atc  ccg tcc atc atg aac  gtc ctc ctc      4014
Asn Ala  Leu Val Gly Ala Ile  Pro Ser Ile Met Asn  Val Leu Leu
    1325                1330                1335

gtc tgc  ctc atc ttc tgg ctc  atc ttc agc atc atg  ggc gtg aac      4059
Val Cys  Leu Ile Phe Trp Leu  Ile Phe Ser Ile Met  Gly Val Asn
    1340                1345                1350

ctc ttt  gcg ggg aag ttt ggg  agg tgc atc aac cag  aca gag gga      4104
Leu Phe  Ala Gly Lys Phe Gly  Arg Cys Ile Asn Gln  Thr Glu Gly
    1355                1360                1365

gac ttg  cct ttg aac tac acc  atc gtg aac aac aag  agc cag tgt      4149
Asp Leu  Pro Leu Asn Tyr Thr  Ile Val Asn Asn Lys  Ser Gln Cys
    1370                1375                1380

gag tcc  ttg aac ttg acc gga  gaa ttg tac tgg acc  aag gtg aaa      4194
Glu Ser  Leu Asn Leu Thr Gly  Glu Leu Tyr Trp Thr  Lys Val Lys
    1385                1390                1395

gtc aac  ttt gac aac gtg ggg  gcc ggg tac ctg gcc  ctt ctg cag      4239
Val Asn  Phe Asp Asn Val Gly  Ala Gly Tyr Leu Ala  Leu Leu Gln
    1400                1405                1410

gtg gca  aca ttt aaa ggc tgg  atg gac att atg tat  gca gct gtg      4284
Val Ala  Thr Phe Lys Gly Trp  Met Asp Ile Met Tyr  Ala Ala Val
    1415                1420                1425

gac tcc  agg ggg tat gaa gag  cag cct cag tgg gaa  tac aac ctc      4329
Asp Ser  Arg Gly Tyr Glu Glu  Gln Pro Gln Trp Glu  Tyr Asn Leu
    1430                1435                1440

tac atg  tac atc tat ttt gtc  att ttc atc atc ttt  ggg tct ttc      4374
Tyr Met  Tyr Ile Tyr Phe Val  Ile Phe Ile Ile Phe  Gly Ser Phe
    1445                1450                1455

ttc acc  ctg aac ctc ttt att  ggt gtc atc att gac  aac ttc aac      4419
Phe Thr  Leu Asn Leu Phe Ile  Gly Val Ile Ile Asp  Asn Phe Asn
    1460                1465                1470

caa cag  aag aaa aag tta ggg  ggc cag gac atc ttc  atg aca gag      4464
Gln Gln  Lys Lys Lys Leu Gly  Gly Gln Asp Ile Phe  Met Thr Glu
    1475                1480                1485

gag cag  aag aag tac tac aat  gcc atg aag aag ctg  ggc tcc aag      4509
Glu Gln  Lys Lys Tyr Tyr Asn  Ala Met Lys Lys Leu  Gly Ser Lys
    1490                1495                1500

aag ccc  cag aag ccc atc cca  cgg ccc ctg aac aag  tac cag ggc      4554
Lys Pro  Gln Lys Pro Ile Pro  Arg Pro Leu Asn Lys  Tyr Gln Gly
    1505                1510                1515

ttc ata  ttc gac att gtg acc  aag cag gcc ttt gac  gtc acc atc      4599
Phe Ile  Phe Asp Ile Val Thr  Lys Gln Ala Phe Asp  Val Thr Ile
    1520                1525                1530

atg ttt  ctg atc tgc ttg aat  atg gtg acc atg atg  gtg gag aca      4644
Met Phe  Leu Ile Cys Leu Asn  Met Val Thr Met Met  Val Glu Thr
    1535                1540                1545
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gat gac  caa agt cct gag aaa  atc aac atc ttg gcc  aag atc aac      4689
Asp Asp  Gln Ser Pro Glu Lys  Ile Asn Ile Leu Ala  Lys Ile Asn
    1550                 1555                 1560

ctg ctc  ttt gtg gcc atc ttc  aca ggc gag tgt att  gtc aag ctg      4734
Leu Leu  Phe Val Ala Ile Phe  Thr Gly Glu Cys Ile  Val Lys Leu
    1565                 1570                 1575

gct gcc  ctg cgc cac tac tac  ttc acc aac agc tgg  aat atc ttc      4779
Ala Ala  Leu Arg His Tyr Tyr  Phe Thr Asn Ser Trp  Asn Ile Phe
    1580                 1585                 1590

gac ttc  gtg gtt gtc atc ctc  tcc atc gtg ggc act  gtg ctc tcg      4824
Asp Phe  Val Val Val Ile Leu  Ser Ile Val Gly Thr  Val Leu Ser
    1595                 1600                 1605

gac atc  atc cag aag tac ttc  ttc tcc ccg acg ctc  ttc cga gtc      4869
Asp Ile  Ile Gln Lys Tyr Phe  Phe Ser Pro Thr Leu  Phe Arg Val
    1610                 1615                 1620

atc cgc  ctg gcc cga ata ggc  cgc atc ctc aga ctg  atc cga ggg      4914
Ile Arg  Leu Ala Arg Ile Gly  Arg Ile Leu Arg Leu  Ile Arg Gly
    1625                 1630                 1635

gcc aag  ggg atc cgc acg ctg  ctc ttt gcc ctc atg  atg tcc ctg      4959
Ala Lys  Gly Ile Arg Thr Leu  Leu Phe Ala Leu Met  Met Ser Leu
    1640                 1645                 1650

cct gcc  ctc ttc aac atc ggg  ctg ctg ctc ttc ctc  gtc atg ttc      5004
Pro Ala  Leu Phe Asn Ile Gly  Leu Leu Leu Phe Leu  Val Met Phe
    1655                 1660                 1665

atc tac  tcc atc ttt ggc atg  gcc aac ttc gct tat  gtc aag tgg      5049
Ile Tyr  Ser Ile Phe Gly Met  Ala Asn Phe Ala Tyr  Val Lys Trp
    1670                 1675                 1680

gag gct  ggc atc gac gac atg  ttc aac ttc cag acc  ttc gcc aac      5094
Glu Ala  Gly Ile Asp Asp Met  Phe Asn Phe Gln Thr  Phe Ala Asn
    1685                 1690                 1695

agc atg  ctg tgc ctc ttc cag  atc acc acg tcg gcc  ggc tgg gat      5139
Ser Met  Leu Cys Leu Phe Gln  Ile Thr Thr Ser Ala  Gly Trp Asp
    1700                 1705                 1710

ggc ctc  ctc agc ccc atc ctc  aac act ggg ccg ccc  tac tgc gac      5184
Gly Leu  Leu Ser Pro Ile Leu  Asn Thr Gly Pro Pro  Tyr Cys Asp
    1715                 1720                 1725

ccc act  ctg ccc aac agc aat  ggc tct cgg ggg gac  tgc ggg agc      5229
Pro Thr  Leu Pro Asn Ser Asn  Gly Ser Arg Gly Asp  Cys Gly Ser
    1730                 1735                 1740

cca gcc  gtg ggc atc ctc ttc  ttc acc acc tac atc  atc atc tcc      5274
Pro Ala  Val Gly Ile Leu Phe  Phe Thr Thr Tyr Ile  Ile Ile Ser
    1745                 1750                 1755

ttc ctc  atc gtg gtc aac atg  tac att gcc atc atc  ctg gag aac      5319
Phe Leu  Ile Val Val Asn Met  Tyr Ile Ala Ile Ile  Leu Glu Asn
    1760                 1765                 1770

ttc agc  gtg gcc acg gag gag  agc acc gag ccc ctg  agt gag gac      5364
Phe Ser  Val Ala Thr Glu Glu  Ser Thr Glu Pro Leu  Ser Glu Asp
    1775                 1780                 1785

gac ttc  gat atg ttc tat gag  atc tgg gag aaa ttt  gac cca gag      5409
Asp Phe  Asp Met Phe Tyr Glu  Ile Trp Glu Lys Phe  Asp Pro Glu
    1790                 1795                 1800

gcc act  cag ttt att gag tat  tcg gtc ctg tct gac  ttt gcc gat      5454
Ala Thr  Gln Phe Ile Glu Tyr  Ser Val Leu Ser Asp  Phe Ala Asp
    1805                 1810                 1815

gcc ctg  tct gag cca ctc cgt  atc gcc aag ccc aac  cag ata agc      5499
Ala Leu  Ser Glu Pro Leu Arg  Ile Ala Lys Pro Asn  Gln Ile Ser
    1820                 1825                 1830

ctc atc  aac atg gac ctg ccc  atg gtg agt ggg gac  cgc atc cat      5544
Leu Ile  Asn Met Asp Leu Pro  Met Val Ser Gly Asp  Arg Ile His
    1835                 1840                 1845
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tgc atg  gac att ctc ttt gcc  ttc acc aaa agg gtc  ctg ggg gag      5589
Cys Met  Asp Ile Leu Phe Ala  Phe Thr Lys Arg Val  Leu Gly Glu
    1850                 1855                 1860

tct ggg  gag atg gac gcc ctg  aag atc cag atg gag  gag aag ttc      5634
Ser Gly  Glu Met Asp Ala Leu  Lys Ile Gln Met Glu  Glu Lys Phe
    1865                 1870                 1875

atg gca  gcc aac cca tcc aag  atc tcc tac gag ccc  atc acc acc      5679
Met Ala  Ala Asn Pro Ser Lys  Ile Ser Tyr Glu Pro  Ile Thr Thr
    1880                 1885                 1890

aca ctc  cgg cgc aag cac gaa  gag gtg tcg gcc atg  gtt atc cag      5724
Thr Leu  Arg Arg Lys His Glu  Glu Val Ser Ala Met  Val Ile Gln
    1895                 1900                 1905

aga gcc  ttc cgc agg cac ctg  ctg caa cgc tct ttg  aag cat gcc      5769
Arg Ala  Phe Arg Arg His Leu  Leu Gln Arg Ser Leu  Lys His Ala
    1910                 1915                 1920

tcc ttc  ctc ttc cgt cag cag  gcg ggc agc ggc ctc  tcc gaa gag      5814
Ser Phe  Leu Phe Arg Gln Gln  Ala Gly Ser Gly Leu  Ser Glu Glu
    1925                 1930                 1935

gat gcc  cct gag cga gag ggc  ctc atc gcc tac gtg  atg agt gag      5859
Asp Ala  Pro Glu Arg Glu Gly  Leu Ile Ala Tyr Val  Met Ser Glu
    1940                 1945                 1950

aac ttc  tcc cga ccc ctt ggc  cca ccc tcc agc tcc  tcc atc tcc      5904
Asn Phe  Ser Arg Pro Leu Gly  Pro Pro Ser Ser Ser  Ser Ile Ser
    1955                 1960                 1965

tcc act  tcc ttc cca ccc tcc  tat gac agt gtc act  aga gcc acc      5949
Ser Thr  Ser Phe Pro Pro Ser  Tyr Asp Ser Val Thr  Arg Ala Thr
    1970                 1975                 1980

agc gat  aac ctc cag gtg cgg  ggg tct gac tac agc  cac agt gaa      5994
Ser Asp  Asn Leu Gln Val Arg  Gly Ser Asp Tyr Ser  His Ser Glu
    1985                 1990                 1995

gat ctc  gcc gac ttc ccc cct  tct ccg gac agg gac  cgt gag tcc      6039
Asp Leu  Ala Asp Phe Pro Pro  Ser Pro Asp Arg Asp  Arg Glu Ser
    2000                 2005                 2010

atc gtg  tgagcctcgg cctggctggc caggacacac tgaaaagcag ccttttttcac     6095
Ile Val
    2015

catggcaaac ctaaatgcag tcagtcamaa accagcctgg ggccttcctg gctttgggag   6155
taagaaatgg gcct                                                     6169


<210> SEQ ID NO 6
<211> LENGTH: 2015
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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

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

Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
        35                  40                  45

Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
    50                  55                  60

Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
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           100                 105                 110

Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140

Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285

Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320

Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525
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Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His His Thr Ser
545                 550                 555                 560

Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
                565                 570                 575

Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605

Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670

Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
    850                 855                 860

Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895

Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940
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Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
945                 950                 955                 960

Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990

Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                 1000                1005

Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

Thr Glu  Glu Glu Ser Ser Lys  Gln Glu Ser Gln Pro  Val Ser Gly
    1070                1075                1080

Gly Pro  Glu Ala Pro Pro Asp  Ser Arg Thr Trp Ser  Gln Val Ser
    1085                1090                1095

Ala Thr  Ala Ser Ser Glu Ala  Glu Ala Ser Ala Ser  Gln Ala Asp
    1100                1105                1110

Trp Arg  Gln Gln Trp Lys Ala  Glu Pro Gln Ala Pro  Gly Cys Gly
    1115                1120                1125

Glu Thr  Pro Glu Asp Ser Cys  Ser Glu Gly Ser Thr  Ala Asp Met
    1130                1135                1140

Thr Asn  Thr Ala Glu Leu Leu  Glu Gln Ile Pro Asp  Leu Gly Gln
    1145                1150                1155

Asp Val  Lys Asp Pro Glu Asp  Cys Phe Thr Glu Gly  Cys Val Arg
    1160                1165                1170

Arg Cys  Pro Cys Cys Ala Val  Asp Thr Thr Gln Ala  Pro Gly Lys
    1175                1180                1185

Val Trp  Trp Arg Leu Arg Lys  Thr Cys Tyr His Ile  Val Glu His
    1190                1195                1200

Ser Trp  Phe Glu Thr Phe Ile  Ile Phe Met Ile Leu  Leu Ser Ser
    1205                1210                1215

Gly Ala  Leu Ala Phe Glu Asp  Ile Tyr Leu Glu Glu  Arg Lys Thr
    1220                1225                1230

Ile Lys  Val Leu Leu Glu Tyr  Ala Asp Lys Met Phe  Thr Tyr Val
    1235                1240                1245

Phe Val  Leu Glu Met Leu Leu  Lys Trp Val Ala Tyr  Gly Phe Lys
    1250                1255                1260

Lys Tyr  Phe Thr Asn Ala Trp  Cys Trp Leu Asp Phe  Leu Ile Val
    1265                1270                1275

Asp Val  Ser Leu Val Ser Leu  Val Ala Asn Thr Leu  Gly Phe Ala
    1280                1285                1290

Glu Met  Gly Pro Ile Lys Ser  Leu Arg Thr Leu Arg  Ala Leu Arg
    1295                1300                1305

Pro Leu  Arg Ala Leu Ser Arg  Phe Glu Gly Met Arg  Val Val Val
    1310                1315                1320

Asn Ala  Leu Val Gly Ala Ile  Pro Ser Ile Met Asn  Val Leu Leu
    1325                1330                1335

Val Cys  Leu Ile Phe Trp Leu  Ile Phe Ser Ile Met  Gly Val Asn
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    1340                1345                1350

Leu Phe  Ala Gly Lys Phe Gly  Arg Cys Ile Asn Gln  Thr Glu Gly
    1355                1360                1365

Asp Leu  Pro Leu Asn Tyr Thr  Ile Val Asn Asn Lys  Ser Gln Cys
    1370                1375                1380

Glu Ser  Leu Asn Leu Thr Gly  Glu Leu Tyr Trp Thr  Lys Val Lys
    1385                1390                1395

Val Asn  Phe Asp Asn Val Gly  Ala Gly Tyr Leu Ala  Leu Leu Gln
    1400                1405                1410

Val Ala  Thr Phe Lys Gly Trp  Met Asp Ile Met Tyr  Ala Ala Val
    1415                1420                1425

Asp Ser  Arg Gly Tyr Glu Glu  Gln Pro Gln Trp Glu  Tyr Asn Leu
    1430                1435                1440

Tyr Met  Tyr Ile Tyr Phe Val  Ile Phe Ile Ile Phe  Gly Ser Phe
    1445                1450                1455

Phe Thr  Leu Asn Leu Phe Ile  Gly Val Ile Ile Asp  Asn Phe Asn
    1460                1465                1470

Gln Gln  Lys Lys Lys Leu Gly  Gly Gln Asp Ile Phe  Met Thr Glu
    1475                1480                1485

Glu Gln  Lys Lys Tyr Tyr Asn  Ala Met Lys Lys Leu  Gly Ser Lys
    1490                1495                1500

Lys Pro  Gln Lys Pro Ile Pro  Arg Pro Leu Asn Lys  Tyr Gln Gly
    1505                1510                1515

Phe Ile  Phe Asp Ile Val Thr  Lys Gln Ala Phe Asp  Val Thr Ile
    1520                1525                1530

Met Phe  Leu Ile Cys Leu Asn  Met Val Thr Met Met  Val Glu Thr
    1535                1540                1545

Asp Asp  Gln Ser Pro Glu Lys  Ile Asn Ile Leu Ala  Lys Ile Asn
    1550                1555                1560

Leu Leu  Phe Val Ala Ile Phe  Thr Gly Glu Cys Ile  Val Lys Leu
    1565                1570                1575

Ala Ala  Leu Arg His Tyr Tyr  Phe Thr Asn Ser Trp  Asn Ile Phe
    1580                1585                1590

Asp Phe  Val Val Val Ile Leu  Ser Ile Val Gly Thr  Val Leu Ser
    1595                1600                1605

Asp Ile  Ile Gln Lys Tyr Phe  Phe Ser Pro Thr Leu  Phe Arg Val
    1610                1615                1620

Ile Arg  Leu Ala Arg Ile Gly  Arg Ile Leu Arg Leu  Ile Arg Gly
    1625                1630                1635

Ala Lys  Gly Ile Arg Thr Leu  Leu Phe Ala Leu Met  Met Ser Leu
    1640                1645                1650

Pro Ala  Leu Phe Asn Ile Gly  Leu Leu Leu Phe Leu  Val Met Phe
    1655                1660                1665

Ile Tyr  Ser Ile Phe Gly Met  Ala Asn Phe Ala Tyr  Val Lys Trp
    1670                1675                1680

Glu Ala  Gly Ile Asp Asp Met  Phe Asn Phe Gln Thr  Phe Ala Asn
    1685                1690                1695

Ser Met  Leu Cys Leu Phe Gln  Ile Thr Thr Ser Ala  Gly Trp Asp
    1700                1705                1710

Gly Leu  Leu Ser Pro Ile Leu  Asn Thr Gly Pro Pro  Tyr Cys Asp
    1715                1720                1725

Pro Thr  Leu Pro Asn Ser Asn  Gly Ser Arg Gly Asp  Cys Gly Ser
    1730                1735                1740
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Pro Ala  Val Gly Ile Leu Phe  Phe Thr Thr Tyr Ile  Ile Ile Ser
    1745                1750                1755

Phe Leu  Ile Val Val Asn Met  Tyr Ile Ala Ile Ile  Leu Glu Asn
    1760                1765                1770

Phe Ser  Val Ala Thr Glu Glu  Ser Thr Glu Pro Leu  Ser Glu Asp
    1775                1780                1785

Asp Phe  Asp Met Phe Tyr Glu  Ile Trp Glu Lys Phe  Asp Pro Glu
    1790                1795                1800

Ala Thr  Gln Phe Ile Glu Tyr  Ser Val Leu Ser Asp  Phe Ala Asp
    1805                1810                1815

Ala Leu  Ser Glu Pro Leu Arg  Ile Ala Lys Pro Asn  Gln Ile Ser
    1820                1825                1830

Leu Ile  Asn Met Asp Leu Pro  Met Val Ser Gly Asp  Arg Ile His
    1835                1840                1845

Cys Met  Asp Ile Leu Phe Ala  Phe Thr Lys Arg Val  Leu Gly Glu
    1850                1855                1860

Ser Gly  Glu Met Asp Ala Leu  Lys Ile Gln Met Glu  Glu Lys Phe
    1865                1870                1875

Met Ala  Ala Asn Pro Ser Lys  Ile Ser Tyr Glu Pro  Ile Thr Thr
    1880                1885                1890

Thr Leu  Arg Arg Lys His Glu  Glu Val Ser Ala Met  Val Ile Gln
    1895                1900                1905

Arg Ala  Phe Arg Arg His Leu  Leu Gln Arg Ser Leu  Lys His Ala
    1910                1915                1920

Ser Phe  Leu Phe Arg Gln Gln  Ala Gly Ser Gly Leu  Ser Glu Glu
    1925                1930                1935

Asp Ala  Pro Glu Arg Glu Gly  Leu Ile Ala Tyr Val  Met Ser Glu
    1940                1945                1950

Asn Phe  Ser Arg Pro Leu Gly  Pro Pro Ser Ser Ser  Ser Ile Ser
    1955                1960                1965

Ser Thr  Ser Phe Pro Pro Ser  Tyr Asp Ser Val Thr  Arg Ala Thr
    1970                1975                1980

Ser Asp  Asn Leu Gln Val Arg  Gly Ser Asp Tyr Ser  His Ser Glu
    1985                1990                1995

Asp Leu  Ala Asp Phe Pro Pro  Ser Pro Asp Arg Asp  Arg Glu Ser
    2000                2005                2010

Ile Val
    2015
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<210> SEQ ID NO 7
<211> LENGTH: 6169
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(6045)

<400> SEQUENCE: 7

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atg gca aac ttc cta tta cct agg ggc acc agc agc ttc cgc agg ttc       48
Met Ala Asn Phe Leu Leu Pro Arg Gly Thr Ser Ser Phe Arg Arg Phe
1               5                  10                  15

aca cgg gag tcc ctg gca gcc atc gag aag cgc atg gcg gag aag caa       96
Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln
            20                  25                  30

gcc cgc ggc tca acc acc ttg cag gag agc cga gag ggg ctg ccc gag      144
Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
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        35                  40                  45

gag gag gct ccc cgg ccc cag ctg gac ctg cag gcc tcc aaa aag ctg      192
Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
    50                  55                  60

cca gat ctc tat ggc aat cca ccc caa gag ctc atc gga gag ccc ctg      240
Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

gag gac ctg gac ccc ttc tat agc acc caa aag act ttc atc gta ctg      288
Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

aat aaa ggc aag acc atc ttc cgg ttc agt gcc acc aac gcc ttg tat      336
Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
            100                 105                 110

gtc ctc agt ccc ttc cac ccc atc cgg aga gcg gct gtg aag att ctg      384
Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

gtt cac tcg ctc ttc aac atg ctc atc atg tgc acc atc ctc acc aac      432
Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140

tgc gtg ttc atg gcc cag cac gac cct cca ccc tgg acc aag tat gtc      480
Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

gag tac acc ttc acc gcc att tac acc ttt gag tct ctg gtc aag att      528
Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

ctg gct cga ggc ttc tgc ctg cac gcg ttc act ttc ctt cgg gac cca      576
Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

tgg aac tgg ctg gac ttt agt gtg att atc atg gca tac aca act gaa      624
Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

ttt gtg gac ctg ggc aat gtc tca gcc tta cgc acc ttc cga gtc ctc      672
Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

cgg gcc ctg aaa act ata tca gtc att tca ggg ctg aag acc atc gtg      720
Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

ggg gcc ctg atc cag tct gtg aag aag ctg gct gat gtg atg gtc ctc      768
Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

aca gtc ttc tgc ctc agc gtc ttt gcc ctc atc ggc ctg cag ctc ttc      816
Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

atg ggc aac cta agg cac aag tgc gtg cgc aac ttc aca gcg ctc aac      864
Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285

ggc acc aac ggc tcc gtg gag gcc gac ggc ttg gtc tgg gaa tcc ctg      912
Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

gac ctt tac ctc agt gat cca gaa aat tac ctg ctc aag aac ggc acc      960
Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320

tct gat gtg tta ctg tgt ggg aac agc tct gac gct ggg aca tgt ccg     1008
Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

gag ggc tac cgg tgc cta aag gca ggc gag aac ccc gac cac ggc tac     1056
Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

acc agc ttc gat tcc ttt gcc tgg gcc ttt ctt gca ctc ttc cgc ctg     1104
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Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

atg acg cag gac tgc tgg gag cgc ctc tat cag cag acc ctc agg tcc     1152
Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

gca ggg aag atc tac atg atc ttc ttc atg ctt gtc atc ttc ctg ggg     1200
Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

tcc ttc tac ctg gtg aac ctg atc ctg gcc gtg gtc gca atg gcc tat     1248
Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

gag gag caa aac caa gcc acc atc gct gag acc gag gag aag gaa aag     1296
Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

cgc ttc cag gag gcc atg gaa atg ctc aag aaa gaa cac gag gcc ctc     1344
Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

acc atc agg ggt gtg gat acc gtg tcc cgt agc tcc ttg gag atg tcc     1392
Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

cct ttg gcc cca gta aac agc cat gag aga aga agc aag agg aga aaa     1440
Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

cgg atg tct tca gga act gag gag tgt ggg gag gac agg ctc ccc aag     1488
Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

tct gac tca gaa gat ggt ccc aga gca atg aat cat ctc agc ctc acc     1536
Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

cgt ggc ctc agc agg act tct atg aag cca cgt tcc agc cgc ggg agc     1584
Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

att ttc acc ttt cgc agg cga gac ctg ggt tct gaa gca gat ttt gca     1632
Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

gat gat gaa aac agc aca gcg ggg gag agc gag agc cac cgc aca tca     1680
Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His Arg Thr Ser
545                 550                 555                 560

ctg ctg gtg ccc tgg ccc ctg cgc cgg acc agt gcc cag gga cag ccc     1728
Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
                565                 570                 575

agt ccc gga acc tcg gct cct ggc cac gcc ctc cat ggc aaa aag aac     1776
Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

agc act gtg gac tgc aat ggg gtg gtc tca tta ctg ggg gca ggc gac     1824
Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605

cca gag gcc aca tcc cca gga agc cac ctc ctc cgc cct gtg atg cta     1872
Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

gag cac ccg cca gac acg acc acg cca tcg gag gag cca ggc ggg ccc     1920
Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

cag atg ctg acc tcc cag gct ccg tgt gta gat ggc ttc gag gag cca     1968
Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

gga gca cgg cag cgg gcc ctc agc gca gtc agc gtc ctc acc agc gca     2016
Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670
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ctg gaa gag tta gag gag tct cgc cac aag tgt cca cca tgc tgg aac     2064
Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

cgt ctc gcc cag cgc tac ctg atc tgg gag tgc tgc ccg ctg tgg atg     2112
Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

tcc atc aag cag gga gtg aag ttg gtg gtc atg gac ccg ttt act gac     2160
Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

ctc acc atc act atg tgc atc gta ctc aac aca ctc ttc atg gcg ctg     2208
Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

gag cac tac aac atg aca agt gaa ttc gag gag atg ctg cag gtc gga     2256
Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

aac ctg gtc ttc aca ggg att ttc aca gca gag atg acc ttc aag atc     2304
Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

att gcc ctc gac ccc tac tac tac ttc caa cag ggc tgg aac atc ttc     2352
Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

gac agc atc atc gtc atc ctt agc ctc atg gag ctg ggc ctg tcc cgc     2400
Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

atg agc aac ttg tcg gtg ctg cgc tcc ttc cgc ctg ctg cgg gtc ttc     2448
Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

aag ctg gcc aaa tca tgg ccc acc ctg aac aca ctc atc aag atc atc     2496
Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

ggg aac tca gtg ggg gca ctg ggg aac ctg aca ctg gtg cta gcc atc     2544
Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

atc gtg ttc atc ttt gct gtg gtg ggc atg cag ctc ttt ggc aag aac     2592
Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
    850                 855                 860

tac tcg gag ctg agg gac agc gac tca ggc ctg ctg cct cgc tgg cac     2640
Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

atg atg gac ttc ttt cat gcc ttc ctc atc atc ttc cgc atc ctc tgt     2688
Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895

gga gag tgg atc gag acc atg tgg gac tgc atg gag gtg tcg ggg cag     2736
Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

tca tta tgc ctg ctg gtc ttc ttg ctt gtt atg gtc att ggc aac ctt     2784
Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

gtg gtc ctg aat ctc ttc ctg gcc ttg ctg ctc agc tcc ttc agt gca     2832
Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

gac aac ctc aca gcc cct gat gag gac aga gag atg aac aac ctc cag     2880
Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
945                 950                 955                 960

ctg gcc ctg gcc cgc atc cag agg ggc ctg cgc ttt gtc aag cgg acc     2928
Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

acc tgg gat ttc tgc tgt ggt ctc ctg cgg cag cgg cct cag aag ccc     2976
Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990
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gca gcc ctt gcc gcc cag ggc cag  ctg ccc agc tgc att  gcc acc ccc   3024
Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                1000                1005

tac tcc  ccg cca ccc cca gag  acg gag aag gtg cct  ccc acc cgc      3069
Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

aag gaa  aca cgg ttt gag gaa  ggc gag caa cca ggc  cag ggc acc      3114
Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

ccc ggg  gat cca gag ccc gtg  tgt gtg ccc atc gct  gtg gcc gag      3159
Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

tca gac  aca gat gac caa gaa  gaa gat gag gag aac  agc ctg ggc      3204
Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

acg gag  gag gag tcc agc aag  cag gaa tcc cag cct  gtg tcc ggt      3249
Thr Glu  Glu Glu Ser Ser Lys  Gln Glu Ser Gln Pro  Val Ser Gly
    1070                1075                1080

ggc cca  gag gcc cct ccg gat  tcc agg acc tgg agc  cag gtg tca      3294
Gly Pro  Glu Ala Pro Pro Asp  Ser Arg Thr Trp Ser  Gln Val Ser
    1085                1090                1095

gcg act  gcc tcc tct gag gcc  gag gcc agt gca tct  cag gcc gac      3339
Ala Thr  Ala Ser Ser Glu Ala  Glu Ala Ser Ala Ser  Gln Ala Asp
    1100                1105                1110

tgg cgg  cag cag tgg aaa gcg  gaa ccc cag gcc cca  ggg tgc ggt      3384
Trp Arg  Gln Gln Trp Lys Ala  Glu Pro Gln Ala Pro  Gly Cys Gly
    1115                1120                1125

gag acc  cca gag gac agt tgc  tcc gag ggc agc aca  gca gac atg      3429
Glu Thr  Pro Glu Asp Ser Cys  Ser Glu Gly Ser Thr  Ala Asp Met
    1130                1135                1140

acc aac  acc gct gag ctc ctg  gag cag atc cct gac  ctc ggc cag      3474
Thr Asn  Thr Ala Glu Leu Leu  Glu Gln Ile Pro Asp  Leu Gly Gln
    1145                1150                1155

gat gtc  aag gac cca gag gac  tgc ttc act gaa ggc  tgt gtc cgg      3519
Asp Val  Lys Asp Pro Glu Asp  Cys Phe Thr Glu Gly  Cys Val Arg
    1160                1165                1170

cgc tgt  ccc tgc tgt gcg gtg  gac acc aca cag gcc  cca ggg aag      3564
Arg Cys  Pro Cys Cys Ala Val  Asp Thr Thr Gln Ala  Pro Gly Lys
    1175                1180                1185

gtc tgg  tgg cgg ttg cgc aag  acc tgc tac cac atc  gtg gag cac      3609
Val Trp  Trp Arg Leu Arg Lys  Thr Cys Tyr His Ile  Val Glu His
    1190                1195                1200

agc tgg  ttc gag aca ttc atc  atc ttc atg atc cta  ctc agc agt      3654
Ser Trp  Phe Glu Thr Phe Ile  Ile Phe Met Ile Leu  Leu Ser Ser
    1205                1210                1215

gga gcg  ctg gcc ttc gag gac  atc tac cta gag gag  cgg aag acc      3699
Gly Ala  Leu Ala Phe Glu Asp  Ile Tyr Leu Glu Glu  Arg Lys Thr
    1220                1225                1230

atc aag  gtt ctg ctt gag tat  gcc gac aag atg ttc  aca tat gtc      3744
Ile Lys  Val Leu Leu Glu Tyr  Ala Asp Lys Met Phe  Thr Tyr Val
    1235                1240                1245

ttc gtg  ctg gag atg ctg ctc  aag tgg gtg gcc tac  ggc ttc aag      3789
Phe Val  Leu Glu Met Leu Leu  Lys Trp Val Ala Tyr  Gly Phe Lys
    1250                1255                1260

aag tac  ttc acc aat gcc tgg  tgc tgg ctc gac ttc  ctc atc gta      3834
Lys Tyr  Phe Thr Asn Ala Trp  Cys Trp Leu Asp Phe  Leu Ile Val
    1265                1270                1275

gac gtc  tct ctg gtc agc ctg  gtg gcc aac acc ctg  ggc ttt gcc      3879
Asp Val  Ser Leu Val Ser Leu  Val Ala Asn Thr Leu  Gly Phe Ala
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    1280                1285                1290

gag atg  ggt ccc atc aag tca  ctg cgg acg ctg cgt  gca ctc cgt      3924
Glu Met  Gly Pro Ile Lys Ser  Leu Arg Thr Leu Arg  Ala Leu Arg
    1295                1300                1305

cct ctg  aga gct ctg tca cga  ttt gag ggc atg agg  gtg gtg gtc      3969
Pro Leu  Arg Ala Leu Ser Arg  Phe Glu Gly Met Arg  Val Val Val
    1310                1315                1320

aat gcc  ctg gtg ggc gcc atc  ccg tcc atc atg aac  gtc ctc ctc      4014
Asn Ala  Leu Val Gly Ala Ile  Pro Ser Ile Met Asn  Val Leu Leu
    1325                1330                1335

gtc tgc  ctc atc ttc tgg ctc  atc ttc agc atc atg  ggc gtg aac      4059
Val Cys  Leu Ile Phe Trp Leu  Ile Phe Ser Ile Met  Gly Val Asn
    1340                1345                1350

ctc ttt  gcg ggg aag ttt ggg  agg tgc atc aac cag  aca gag gga      4104
Leu Phe  Ala Gly Lys Phe Gly  Arg Cys Ile Asn Gln  Thr Glu Gly
    1355                1360                1365

gac ttg  cct ttg aac tac acc  atc gtg aac aac aag  agc cag tgt      4149
Asp Leu  Pro Leu Asn Tyr Thr  Ile Val Asn Asn Lys  Ser Gln Cys
    1370                1375                1380

gag tcc  ttg aac ttg acc gga  gaa ttg tac tgg acc  aag gtg aaa      4194
Glu Ser  Leu Asn Leu Thr Gly  Glu Leu Tyr Trp Thr  Lys Val Lys
    1385                1390                1395

gtc aac  ttt gac aac gtg ggg  gcc ggg tac ctg gcc  ctt ctg cag      4239
Val Asn  Phe Asp Asn Val Gly  Ala Gly Tyr Leu Ala  Leu Leu Gln
    1400                1405                1410

gtg gca  aca ttt aaa ggc tgg  atg gac att atg tat  gca gct gtg      4284
Val Ala  Thr Phe Lys Gly Trp  Met Asp Ile Met Tyr  Ala Ala Val
    1415                1420                1425

gac tcc  agg ggg tat gaa gag  cag cct cag tgg gaa  tac aac ctc      4329
Asp Ser  Arg Gly Tyr Glu Glu  Gln Pro Gln Trp Glu  Tyr Asn Leu
    1430                1435                1440

tac atg  tac atc tat ttt gtc  att ttc atc atc ttt  ggg tct ttc      4374
Tyr Met  Tyr Ile Tyr Phe Val  Ile Phe Ile Ile Phe  Gly Ser Phe
    1445                1450                1455

ttc acc  ctg aac ctc ttt att  ggt gtc atc att gac  aac ttc aac      4419
Phe Thr  Leu Asn Leu Phe Ile  Gly Val Ile Ile Asp  Asn Phe Asn
    1460                1465                1470

caa cag  aag aaa aag tta ggg  ggc cag gac atc ttc  atg aca gag      4464
Gln Gln  Lys Lys Lys Leu Gly  Gly Gln Asp Ile Phe  Met Thr Glu
    1475                1480                1485

gag cag  aag aag tac tac aat  gcc atg aag aag ctg  ggc tcc aag      4509
Glu Gln  Lys Lys Tyr Tyr Asn  Ala Met Lys Lys Leu  Gly Ser Lys
    1490                1495                1500

aag ccc  cag aag ccc atc cca  cgg ccc ctg aac aag  tac cag ggc      4554
Lys Pro  Gln Lys Pro Ile Pro  Arg Pro Leu Asn Lys  Tyr Gln Gly
    1505                1510                1515

ttc ata  ttc gac att gtg acc  aag cag gcc ttt gac  gtc acc atc      4599
Phe Ile  Phe Asp Ile Val Thr  Lys Gln Ala Phe Asp  Val Thr Ile
    1520                1525                1530

atg ttt  ctg atc tgc ttg aat  atg gtg acc atg atg  gtg gag aca      4644
Met Phe  Leu Ile Cys Leu Asn  Met Val Thr Met Met  Val Glu Thr
    1535                1540                1545

gat gac  caa agt cct gag aaa  atc aac atc ttg gcc  aag atc aac      4689
Asp Asp  Gln Ser Pro Glu Lys  Ile Asn Ile Leu Ala  Lys Ile Asn
    1550                1555                1560

ctg ctc  ttt gtg gcc atc ttc  aca ggc gag tgt att  gtc aag ctg      4734
Leu Leu  Phe Val Ala Ile Phe  Thr Gly Glu Cys Ile  Val Lys Leu
    1565                1570                1575

gct gcc  ctg cgc cac tac tac  ttc acc aac agc tgg  aat atc ttc      4779
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Ala Ala  Leu Arg His Tyr Tyr  Phe Thr Asn Ser Trp  Asn Ile Phe
    1580                1585                1590

gac ttc  gtg gtt gtc atc ctc  tcc atc gtg ggc act  gtg ctc tcg      4824
Asp Phe  Val Val Val Ile Leu  Ser Ile Val Gly Thr  Val Leu Ser
    1595                1600                1605

gac atc  atc cag aag tac ttc  ttc tcc ccg acg ctc  ttc cga gtc      4869
Asp Ile  Ile Gln Lys Tyr Phe  Phe Ser Pro Thr Leu  Phe Arg Val
    1610                1615                1620

atc cgc  ctg gcc cga ata ggc  cgc atc ctc aga ctg  atc cga ggg      4914
Ile Arg  Leu Ala Arg Ile Gly  Arg Ile Leu Arg Leu  Ile Arg Gly
    1625                1630                1635

gcc aag  ggg atc cgc acg ctg  ctc ttt gcc ctc atg  atg tcc ctg      4959
Ala Lys  Gly Ile Arg Thr Leu  Leu Phe Ala Leu Met  Met Ser Leu
    1640                1645                1650

cct gcc  ctc ttc aac atc ggg  ctg ctg ctc ttc ctc  gtc atg ttc      5004
Pro Ala  Leu Phe Asn Ile Gly  Leu Leu Leu Phe Leu  Val Met Phe
    1655                1660                1665

atc tac  tcc atc ttt ggc atg  gcc aac ttc gct tat  gtc aag tgg      5049
Ile Tyr  Ser Ile Phe Gly Met  Ala Asn Phe Ala Tyr  Val Lys Trp
    1670                1675                1680

gag gct  ggc atc gac gac atg  ttc aac ttc cag acc  ttc gcc aac      5094
Glu Ala  Gly Ile Asp Asp Met  Phe Asn Phe Gln Thr  Phe Ala Asn
    1685                1690                1695

agc atg  ctg tgc ctc ttc cag  atc acc acg tcg gcc  ggc tgg gat      5139
Ser Met  Leu Cys Leu Phe Gln  Ile Thr Thr Ser Ala  Gly Trp Asp
    1700                1705                1710

ggc ctc  ctc agc ccc atc ctc  aac act ggg ccg ccc  tac tgc gac      5184
Gly Leu  Leu Ser Pro Ile Leu  Asn Thr Gly Pro Pro  Tyr Cys Asp
    1715                1720                1725

ccc act  ctg ccc aac agc aat  ggc tct cgg ggg gac  tgc ggg agc      5229
Pro Thr  Leu Pro Asn Ser Asn  Gly Ser Arg Gly Asp  Cys Gly Ser
    1730                1735                1740

cca gcc  gtg ggc atc ctc ttc  ttc acc acc tac atc  atc atc tcc      5274
Pro Ala  Val Gly Ile Leu Phe  Phe Thr Thr Tyr Ile  Ile Ile Ser
    1745                1750                1755

ttc ctc  atc gtg gtc aac atg  tac att gcc atc atc  ctg gag aac      5319
Phe Leu  Ile Val Val Asn Met  Tyr Ile Ala Ile Ile  Leu Glu Asn
    1760                1765                1770

ttc agc  gtg gcc acg gag gag  agc acc gag ccc ctg  agt gag gac      5364
Phe Ser  Val Ala Thr Glu Glu  Ser Thr Glu Pro Leu  Ser Glu Asp
    1775                1780                1785

gac ttc  gat atg ttc tat gag  atc tgg gag aaa ttt  gac cca gag      5409
Asp Phe  Asp Met Phe Tyr Glu  Ile Trp Glu Lys Phe  Asp Pro Glu
    1790                1795                1800

gcc act  cag ttt att gag tat  tcg gtc ctg tct gac  ttt gcc gat      5454
Ala Thr  Gln Phe Ile Glu Tyr  Ser Val Leu Ser Asp  Phe Ala Asp
    1805                1810                1815

gcc ctg  tct gag cca ctc cgt  atc gcc aag ccc aac  cag ata agc      5499
Ala Leu  Ser Glu Pro Leu Arg  Ile Ala Lys Pro Asn  Gln Ile Ser
    1820                1825                1830

ctc atc  aac atg gac ctg ccc  atg gtg agt ggg gac  cgc atc cat      5544
Leu Ile  Asn Met Asp Leu Pro  Met Val Ser Gly Asp  Arg Ile His
    1835                1840                1845

tgc atg  gac att ctc ttt gcc  ttc acc aaa agg gtc  ctg ggg gag      5589
Cys Met  Asp Ile Leu Phe Ala  Phe Thr Lys Arg Val  Leu Gly Glu
    1850                1855                1860

tct ggg  gag atg gac gcc ctg  aag atc cag atg gag  gag aag ttc      5634
Ser Gly  Glu Met Asp Ala Leu  Lys Ile Gln Met Glu  Glu Lys Phe
    1865                1870                1875
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atg gca  gcc aac cca tcc aag  atc tcc tac gag ccc  atc acc acc      5679
Met Ala  Ala Asn Pro Ser Lys  Ile Ser Tyr Glu Pro  Ile Thr Thr
    1880                 1885                 1890

aca ctc  cgg cgc aag cac gaa  gag gtg tcg gcc atg  gtt atc cag      5724
Thr Leu  Arg Arg Lys His Glu  Glu Val Ser Ala Met  Val Ile Gln
    1895                 1900                 1905

aga gcc  ttc cgc agg cac ctg  ctg caa cgc tct ttg  aag cat gcc      5769
Arg Ala  Phe Arg Arg His Leu  Leu Gln Arg Ser Leu  Lys His Ala
    1910                 1915                 1920

tcc ttc  ctc ttc cgt cag cag  gcg ggc agc ggc ctc  tcc gaa gag      5814
Ser Phe  Leu Phe Arg Gln Gln  Ala Gly Ser Gly Leu  Ser Glu Glu
    1925                 1930                 1935

gat gcc  cct gag cga gag ggc  ctc atc gcc tac gtg  atg agt gag      5859
Asp Ala  Pro Glu Arg Glu Gly  Leu Ile Ala Tyr Val  Met Ser Glu
    1940                 1945                 1950

aac ttc  tcc cga ccc ctt ggc  cca ccc tcc agc tcc  tcc atc tcc      5904
Asn Phe  Ser Arg Pro Leu Gly  Pro Pro Ser Ser Ser  Ser Ile Ser
    1955                 1960                 1965

tcc act  tcc ttc cca ccc tcc  tat gac agt gtc act  aga gcc acc      5949
Ser Thr  Ser Phe Pro Pro Ser  Tyr Asp Ser Val Thr  Arg Ala Thr
    1970                 1975                 1980

agc gat  aac ctc cag gtg cgg  ggg tct gac tac agc  cac agt gaa      5994
Ser Asp  Asn Leu Gln Val Arg  Gly Ser Asp Tyr Ser  His Ser Glu
    1985                 1990                 1995

gat ctc  gcc gac ttc ccc cct  tct ccg gac agg gac  cgt gag tcc      6039
Asp Leu  Ala Asp Phe Pro Pro  Ser Pro Asp Arg Asp  Arg Glu Ser
    2000                 2005                 2010

atc gtg  tgagcctcgg cctggctggc caggacacac tgaaaagcag ccttttttcac     6095
Ile Val
    2015

catggcaaac ctaaatgcag tcagtcamaa accagcctgg ggccttcctg gctttgggag   6155

taagaaatgg gcct                                                     6169


<210> SEQ ID NO 8
<211> LENGTH: 2015
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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

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

Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu
        35                  40                  45

Glu Glu Ala Pro Arg Pro Gln Leu Asp Leu Gln Ala Ser Lys Lys Leu
    50                  55                  60

Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65                  70                  75                  80

Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
                85                  90                  95

Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
            100                 105                 110

Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
        115                 120                 125

Val His Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn
    130                 135                 140
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Cys Val Phe Met Ala Gln His Asp Pro Pro Pro Trp Thr Lys Tyr Val
145                 150                 155                 160

Glu Tyr Thr Phe Thr Ala Ile Tyr Thr Phe Glu Ser Leu Val Lys Ile
                165                 170                 175

Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro
            180                 185                 190

Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu
        195                 200                 205

Phe Val Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu
    210                 215                 220

Arg Ala Leu Lys Thr Ile Ser Val Ile Ser Gly Leu Lys Thr Ile Val
225                 230                 235                 240

Gly Ala Leu Ile Gln Ser Val Lys Lys Leu Ala Asp Val Met Val Leu
                245                 250                 255

Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
            260                 265                 270

Met Gly Asn Leu Arg His Lys Cys Val Arg Asn Phe Thr Ala Leu Asn
        275                 280                 285

Gly Thr Asn Gly Ser Val Glu Ala Asp Gly Leu Val Trp Glu Ser Leu
    290                 295                 300

Asp Leu Tyr Leu Ser Asp Pro Glu Asn Tyr Leu Leu Lys Asn Gly Thr
305                 310                 315                 320

Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
                325                 330                 335

Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
            340                 345                 350

Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
        355                 360                 365

Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
    370                 375                 380

Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
385                 390                 395                 400

Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr
                405                 410                 415

Glu Glu Gln Asn Gln Ala Thr Ile Ala Glu Thr Glu Glu Lys Glu Lys
            420                 425                 430

Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
        435                 440                 445

Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
    450                 455                 460

Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
465                 470                 475                 480

Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
                485                 490                 495

Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
            500                 505                 510

Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Arg Gly Ser
        515                 520                 525

Ile Phe Thr Phe Arg Arg Arg Asp Leu Gly Ser Glu Ala Asp Phe Ala
    530                 535                 540

Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His Arg Thr Ser
545                 550                 555                 560

Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro
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               565                 570                 575

Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn
            580                 585                 590

Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
        595                 600                 605

Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
    610                 615                 620

Glu His Pro Pro Asp Thr Thr Thr Pro Ser Glu Glu Pro Gly Gly Pro
625                 630                 635                 640

Gln Met Leu Thr Ser Gln Ala Pro Cys Val Asp Gly Phe Glu Glu Pro
                645                 650                 655

Gly Ala Arg Gln Arg Ala Leu Ser Ala Val Ser Val Leu Thr Ser Ala
            660                 665                 670

Leu Glu Glu Leu Glu Glu Ser Arg His Lys Cys Pro Pro Cys Trp Asn
        675                 680                 685

Arg Leu Ala Gln Arg Tyr Leu Ile Trp Glu Cys Cys Pro Leu Trp Met
    690                 695                 700

Ser Ile Lys Gln Gly Val Lys Leu Val Val Met Asp Pro Phe Thr Asp
705                 710                 715                 720

Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
                725                 730                 735

Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
            740                 745                 750

Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Thr Phe Lys Ile
        755                 760                 765

Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
    770                 775                 780

Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg
785                 790                 795                 800

Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe
                805                 810                 815

Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
            820                 825                 830

Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile
        835                 840                 845

Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn
    850                 855                 860

Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
865                 870                 875                 880

Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
                885                 890                 895

Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
            900                 905                 910

Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
        915                 920                 925

Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala
    930                 935                 940

Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln
945                 950                 955                 960

Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr
                965                 970                 975

Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
            980                 985                 990
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Ala Ala Leu Ala Ala Gln Gly Gln  Leu Pro Ser Cys Ile  Ala Thr Pro
        995                1000                1005

Tyr Ser  Pro Pro Pro Pro Glu  Thr Glu Lys Val Pro  Pro Thr Arg
    1010                1015                1020

Lys Glu  Thr Arg Phe Glu Glu  Gly Glu Gln Pro Gly  Gln Gly Thr
    1025                1030                1035

Pro Gly  Asp Pro Glu Pro Val  Cys Val Pro Ile Ala  Val Ala Glu
    1040                1045                1050

Ser Asp  Thr Asp Asp Gln Glu  Glu Asp Glu Glu Asn  Ser Leu Gly
    1055                1060                1065

Thr Glu  Glu Glu Ser Ser Lys  Gln Glu Ser Gln Pro  Val Ser Gly
    1070                1075                1080

Gly Pro  Glu Ala Pro Pro Asp  Ser Arg Thr Trp Ser  Gln Val Ser
    1085                1090                1095

Ala Thr  Ala Ser Ser Glu Ala  Glu Ala Ser Ala Ser  Gln Ala Asp
    1100                1105                1110

Trp Arg  Gln Gln Trp Lys Ala  Glu Pro Gln Ala Pro  Gly Cys Gly
    1115                1120                1125

Glu Thr  Pro Glu Asp Ser Cys  Ser Glu Gly Ser Thr  Ala Asp Met
    1130                1135                1140

Thr Asn  Thr Ala Glu Leu Leu  Glu Gln Ile Pro Asp  Leu Gly Gln
    1145                1150                1155

Asp Val  Lys Asp Pro Glu Asp  Cys Phe Thr Glu Gly  Cys Val Arg
    1160                1165                1170

Arg Cys  Pro Cys Cys Ala Val  Asp Thr Thr Gln Ala  Pro Gly Lys
    1175                1180                1185

Val Trp  Trp Arg Leu Arg Lys  Thr Cys Tyr His Ile  Val Glu His
    1190                1195                1200

Ser Trp  Phe Glu Thr Phe Ile  Ile Phe Met Ile Leu  Leu Ser Ser
    1205                1210                1215

Gly Ala  Leu Ala Phe Glu Asp  Ile Tyr Leu Glu Glu  Arg Lys Thr
    1220                1225                1230

Ile Lys  Val Leu Leu Glu Tyr  Ala Asp Lys Met Phe  Thr Tyr Val
    1235                1240                1245

Phe Val  Leu Glu Met Leu Leu  Lys Trp Val Ala Tyr  Gly Phe Lys
    1250                1255                1260

Lys Tyr  Phe Thr Asn Ala Trp  Cys Trp Leu Asp Phe  Leu Ile Val
    1265                1270                1275

Asp Val  Ser Leu Val Ser Leu  Val Ala Asn Thr Leu  Gly Phe Ala
    1280                1285                1290

Glu Met  Gly Pro Ile Lys Ser  Leu Arg Thr Leu Arg  Ala Leu Arg
    1295                1300                1305

Pro Leu  Arg Ala Leu Ser Arg  Phe Glu Gly Met Arg  Val Val Val
    1310                1315                1320

Asn Ala  Leu Val Gly Ala Ile  Pro Ser Ile Met Asn  Val Leu Leu
    1325                1330                1335

Val Cys  Leu Ile Phe Trp Leu  Ile Phe Ser Ile Met  Gly Val Asn
    1340                1345                1350

Leu Phe  Ala Gly Lys Phe Gly  Arg Cys Ile Asn Gln  Thr Glu Gly
    1355                1360                1365

Asp Leu  Pro Leu Asn Tyr Thr  Ile Val Asn Asn Lys  Ser Gln Cys
    1370                1375                1380
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Glu Ser  Leu Asn Leu Thr Gly  Glu Leu Tyr Trp Thr  Lys Val Lys
    1385                1390                1395

Val Asn  Phe Asp Asn Val Gly  Ala Gly Tyr Leu Ala  Leu Leu Gln
    1400                1405                1410

Val Ala  Thr Phe Lys Gly Trp  Met Asp Ile Met Tyr  Ala Ala Val
    1415                1420                1425

Asp Ser  Arg Gly Tyr Glu Glu  Gln Pro Gln Trp Glu  Tyr Asn Leu
    1430                1435                1440

Tyr Met  Tyr Ile Tyr Phe Val  Ile Phe Ile Ile Phe  Gly Ser Phe
    1445                1450                1455

Phe Thr  Leu Asn Leu Phe Ile  Gly Val Ile Ile Asp  Asn Phe Asn
    1460                1465                1470

Gln Gln  Lys Lys Lys Leu Gly  Gly Gln Asp Ile Phe  Met Thr Glu
    1475                1480                1485

Glu Gln  Lys Lys Tyr Tyr Asn  Ala Met Lys Lys Leu  Gly Ser Lys
    1490                1495                1500

Lys Pro  Gln Lys Pro Ile Pro  Arg Pro Leu Asn Lys  Tyr Gln Gly
    1505                1510                1515

Phe Ile  Phe Asp Ile Val Thr  Lys Gln Ala Phe Asp  Val Thr Ile
    1520                1525                1530

Met Phe  Leu Ile Cys Leu Asn  Met Val Thr Met Met  Val Glu Thr
    1535                1540                1545

Asp Asp  Gln Ser Pro Glu Lys  Ile Asn Ile Leu Ala  Lys Ile Asn
    1550                1555                1560

Leu Leu  Phe Val Ala Ile Phe  Thr Gly Glu Cys Ile  Val Lys Leu
    1565                1570                1575

Ala Ala  Leu Arg His Tyr Tyr  Phe Thr Asn Ser Trp  Asn Ile Phe
    1580                1585                1590

Asp Phe  Val Val Val Ile Leu  Ser Ile Val Gly Thr  Val Leu Ser
    1595                1600                1605

Asp Ile  Ile Gln Lys Tyr Phe  Phe Ser Pro Thr Leu  Phe Arg Val
    1610                1615                1620

Ile Arg  Leu Ala Arg Ile Gly  Arg Ile Leu Arg Leu  Ile Arg Gly
    1625                1630                1635

Ala Lys  Gly Ile Arg Thr Leu  Leu Phe Ala Leu Met  Met Ser Leu
    1640                1645                1650

Pro Ala  Leu Phe Asn Ile Gly  Leu Leu Leu Phe Leu  Val Met Phe
    1655                1660                1665

Ile Tyr  Ser Ile Phe Gly Met  Ala Asn Phe Ala Tyr  Val Lys Trp
    1670                1675                1680

Glu Ala  Gly Ile Asp Asp Met  Phe Asn Phe Gln Thr  Phe Ala Asn
    1685                1690                1695

Ser Met  Leu Cys Leu Phe Gln  Ile Thr Thr Ser Ala  Gly Trp Asp
    1700                1705                1710

Gly Leu  Leu Ser Pro Ile Leu  Asn Thr Gly Pro Pro  Tyr Cys Asp
    1715                1720                1725

Pro Thr  Leu Pro Asn Ser Asn  Gly Ser Arg Gly Asp  Cys Gly Ser
    1730                1735                1740

Pro Ala  Val Gly Ile Leu Phe  Phe Thr Thr Tyr Ile  Ile Ile Ser
    1745                1750                1755

Phe Leu  Ile Val Val Asn Met  Tyr Ile Ala Ile Ile  Leu Glu Asn
    1760                1765                1770

Phe Ser  Val Ala Thr Glu Glu  Ser Thr Glu Pro Leu  Ser Glu Asp
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    1775                1780                1785

Asp Phe  Asp Met Phe Tyr Glu  Ile Trp Glu Lys Phe  Asp Pro Glu
    1790                1795                1800

Ala Thr  Gln Phe Ile Glu Tyr  Ser Val Leu Ser Asp  Phe Ala Asp
    1805                1810                1815

Ala Leu  Ser Glu Pro Leu Arg  Ile Ala Lys Pro Asn  Gln Ile Ser
    1820                1825                1830

Leu Ile  Asn Met Asp Leu Pro  Met Val Ser Gly Asp  Arg Ile His
    1835                1840                1845

Cys Met  Asp Ile Leu Phe Ala  Phe Thr Lys Arg Val  Leu Gly Glu
    1850                1855                1860

Ser Gly  Glu Met Asp Ala Leu  Lys Ile Gln Met Glu  Glu Lys Phe
    1865                1870                1875

Met Ala  Ala Asn Pro Ser Lys  Ile Ser Tyr Glu Pro  Ile Thr Thr
    1880                1885                1890

Thr Leu  Arg Arg Lys His Glu  Glu Val Ser Ala Met  Val Ile Gln
    1895                1900                1905

Arg Ala  Phe Arg Arg His Leu  Leu Gln Arg Ser Leu  Lys His Ala
    1910                1915                1920

Ser Phe  Leu Phe Arg Gln Gln  Ala Gly Ser Gly Leu  Ser Glu Glu
    1925                1930                1935

Asp Ala  Pro Glu Arg Glu Gly  Leu Ile Ala Tyr Val  Met Ser Glu
    1940                1945                1950

Asn Phe  Ser Arg Pro Leu Gly  Pro Pro Ser Ser Ser  Ser Ile Ser
    1955                1960                1965

Ser Thr  Ser Phe Pro Pro Ser  Tyr Asp Ser Val Thr  Arg Ala Thr
    1970                1975                1980

Ser Asp  Asn Leu Gln Val Arg  Gly Ser Asp Tyr Ser  His Ser Glu
    1985                1990                1995

Asp Leu  Ala Asp Phe Pro Pro  Ser Pro Asp Arg Asp  Arg Glu Ser
    2000                2005                2010

Ile Val
    2015


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ggaactgctg atcagtttgg gaga 24

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ctgtatatgt aggtgcctta tacatg 26

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gaggcagtcg ctgacacc 18

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
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<223> OTHER INFORMATION: Acceptor site sequence for exon 18 of SCN5A

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ggggtctttt cagcaggaat cc 22

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<223> OTHER INFORMATION: Unsure about the exact nucleotide from sequencing data
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: Unsure about the exact nucleotide from sequencing data
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<223> OTHER INFORMATION: n is a, c, g, or t
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<223> OTHER INFORMATION: Unsure about the exact nucleotide from sequencing data
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<223> OTHER INFORMATION: Patial sequence of Exon 17 of SCN5A
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<223> OTHER INFORMATION: Patial sequence of Exon 18 of SCN5A

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tgg gca cgg agg gag tcc agc aag cag gaa tcc cag cct gtg tcc 45
Trp Ala Arg Arg Glu Ser Ser Lys Gln Glu Ser Gln Pro Val Ser
1 5 10 15

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<223> OTHER INFORMATION: Patial sequence of Exon 17 of SCN5A
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<222> LOCATION: (27)..(48)
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<210> SEQ ID NO 21

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<211> LENGTH: 57
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<223> OTHER INFORMATION: Partial genomic DNA sequence of SCN5A

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gagtccagca agcaggtggg ccctgggtct tttcagcagg aatcccagcc tgtgtcc 57

We claim

1. An isolated nucleic acid comprising a polynucleotide selected from the group consisting of a polynucleotide that encodes SEQ ID NO:8 or a polynucleotide fully complementary to a polynucleotide that encodes SEQ ID NO:8.

2. An isolated genetic construct comprising the polynucleotide of claim **1** operably linked to a non-native expression control sequence.

3. An isolated cell comprising a polynucleotide selected from the group consisting of a polynucleotide that encodes SEQ ID NO:8 or a polynucleotide fully complementary to a polynucleotide that encodes SEQ ID NO:8, wherein the polynucleotide is operably linked to a non-native expression control sequence.

4. The cell of claim **3**, wherein the polynucleotide comprises nucleotides 1 to 6045 SEQ ID NO:7.

5. The cell of claim **3**, wherein the cell is from a human embryonic kidney cell line.

6. The nucleic acid of claim **1**, wherein the polynucleotide comprises nucleotides 1 to 6045 of SEQ ID NO:7.

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