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(71) Applicant: **WISCONSIN ALUMNI RESEARCH
FOUNDATION** [US/US]; 614 Walnut Street, P.O. Box
7365, Madison, WI 53707-7365 (US).

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(72) Inventors: **MAKIELSKI, Jonathan, C.**; 2738 Richard-
son Street, Fitchburg, WI 53711 (US). **YE, Bin**; 939
Schroll Drive, Forsyth, IL 62535 (US). **ACKERMAN,
Michael, J.**; 716 4th Street SW, Rochester, MN 55902
(US).
(74) Agent: **BERSON, Benneth, J.**; Quarles & Brady LLP,
P.O. Box 2113, Madison, WI 53701-2113 (US).

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(54) Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS

(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.



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SODIUM CHANNEL ALPHA SUBUNIT VARIANTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application Ser. No. 60/401,018, filed on August 2, 2002, which is incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY
SPONSORED RESEARCH OR DEVELOPMENT

[0002] 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

[0003] 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 $\beta 1$, $\beta 2$ and $\beta 3$. 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.

[0004] Human cardiac sodium channels play a critical role in cardiac excitation. hNav1.5, 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.

[0005] 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.).

[0006] 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.

[0007] 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).

[0008] 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.

[0009] 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 $\beta 1$ 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).

[0010] 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.

[0011] 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

[0012] 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.

[0013] 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.

[0014] 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.

[0015] It is an object of the present invention to identify some of the most common forms of a human cardiac sodium channel.

[0016] 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.

[0017] It is an advantage of the present invention that the *SCN5A* amino acid sequences are common in the human population.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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

[0022] 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).

[0023] Fig. 2 shows quantitative analysis of alternatively spliced variant *SCN5A* transcripts that either encodes Q1077 or excludes Q1077 (Q1077del). (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 (Q1077del) 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 Q1077del 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.

[0024] 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

[0025] 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 $G_{Na} = [1 + \exp (V_{1/2}-V)/\kappa]^{-1}$, where $V_{1/2}$ and κ are the mid-point and the slope factor, respectively, and $G_{Na} = I_{Na}/(V-V_{rev})$ where V_{rev} 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 (V_c). 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: $I_{Na} = I_{Na-max} [1 + \exp (V_c-V_{1/2})/\kappa]^{-1}$, where the $V_{1/2}$ and κ are the midpoint and the slope factor, respectively, and V is the membrane potential. (C) Summary data for recovery from inactivation. Recovery from inactivation 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.

[0026] 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] co-expressed with the $\beta 1$ 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 [H558R;Q1077].

[0027] 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

[0028] 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, PC 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.

[0029] 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.

[0030] 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.

[0031] 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, PC 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.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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.

[0036] 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 hNav1.5 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.

[0037] 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.

[0038] 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.

[0039] 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 5x SSC/5x Denhardt's solution/1.0% SDS, and washing in 0.2x SSC/0.1% SDS at

room temperature. Moderately stringent conditions which include washing in 3x SSC at 42°C can also be used.

[0040] 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 α 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.

[0041] 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.

[0042] 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 DIVERSetTM library of 50,000 manually synthesized chemical compounds; the SCREEN-SetTM library of 24,000 manually synthesized chemical compounds; the CNS-SetTM library of 11,000 compounds; the Cherry-PickTM 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.

[0043] 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.

[0044] 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.

[0045] 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 arrhythmias. For instance, if a subject has a high proportion of low-expressing channels such as [H558R], the subject could be predisposed to develop acquired arrhythmias. Also, for a subject that suffers from a sodium channel-related disease, knowing the SCN5A background of the subject can help choose treatment strategies.

[0046] 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.

[0047] 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.

[0048] 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

[0049] *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 - GGAAGTCTGATCAGTTTGGGAGA (SEQ ID NO:12)). PCR amplification reactions for amplicons 12A and 12B were performed in 20 μ L volumes using 50 ng of genomic DNA, 16 pmol of each primer, 200 μ M 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, NJ). 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 μ L volumes using 50 ng of genomic DNA, 16 pmol of each primer (forward primer - GCCCAGGGCCAGCTGCCAGCT (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 MgCl₂, 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, OH) 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.

[0050] *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 RneasyTM Fibrous Tissue Mini kit (Qiagen, Valencia, CA), and first-strand cDNA synthesis was performed in triplicate on 500 ng of total RNA using the iScriptTM cDNA Synthesis kit (BioRad, Hercules, CA) 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 MgCl₂, 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., Cleveland, OH) and sequenced using an automated AB1377 sequencer (Applied Biosystems, Inc., Foster City, CA). 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-³²P 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, IA). 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 phosphorimager 445 SI and ImageQuant v 5.0 software (Molecular Dynamics, Piscataway, NJ) were used for signal quantification of the two alternatively-spliced transcripts.

[0051] *Gene expression, mutagenesis, and nomenclature:* The *SCN5A* clone hH1 (GenBank No. M77235) was kindly provided by Dr. Al George (Gellens, ME et al., *Proc. Natl. Acad. Sci. U.S.A* 89:554-558, 1992, which is herein incorporated by reference in its entirety) in pRCMV (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, ME 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, JT et al., *Hum. Mutat.* 15:7-12, 2000). The variant channels [H558R], [Q1077del], [H558R;Q1077del], [H558R;Q1077del;M1766L], and [Q1077del;M1766L] were made by mutagenesis at appropriate residues by the following method.

[0052] Mutations were generated using Excite® mutagenesis kit (Stratagene, La Jolla, CA) using the protocol suggested by the manufacturer. DNA was isolated and purified with the Qiagen (Valencia, CA) 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, CA) 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 μ g of plasmid DNA was mixed along with 10 μ L of Superfect reagent (Qiagen) into 140 μ L 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, NY). RNA was isolated (RNAisol from LPS, Moonachie, NJ) and screened by RT-PCR analysis. Colonies that tested RT-PCR-positive were then analyzed by voltage clamp.

[0053] *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, CR 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.

[0054] *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, CA) 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 μ l 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 μ l of PBS and incubated with 150 μ l 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 40x objective and 2x 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

[0055] *Sequence comparisons for SCN5A clones and genotyping of control panels:* The sequences of hH1 (Gellens, ME et al., *Proc. Natl. Acad. Sci. U.S.A* 89:554-558, 1992), hH1a (Hartmann, HA 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_v1.5 sequences from full-length cDNA clones (hH1, hH1a, hH1b), genomic sequencing (hH1c) and genomic databases (Celera, IHGSC).

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	R
	559	T	T	T	A	T	T
	618	L	L	L	L	I	L
	1027	R	R	Q	R	R	R
	1077	Q	Q	Q	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%

^aIHGSC = 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).

^bAccession No. = GenBank Nucleotide accession numbers, where available.

^cAA 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 of all 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.

^dA search of Celera human genome database identified the same sequence

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

^fPopulation Frequency = estimated percentage of protein products in the study population that have this sequence.

[0056] 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.

[0057] *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

[0058] *A common alternatively-spliced variant, Q1077del*: The hHl 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, ME 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).

[0059] To answer the question whether SCN5A most commonly has a glutamine (Q) at both amino acid positions 1076 and 1077 as in hHl or only 1076 as in hHla and hHlb, 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 indicating 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. 2A) 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. 2B) 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 $35 \pm 2.0\%$ (range 31-38%, n=20) and the Q1077del transcript was $65 \pm 2.0\%$ (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.

[0060] *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 hHl, hHla, and hHlb 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 hHlc 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).

[0061] *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 hHl contemporaneously under the same conditions with these variants because most previous studies in the literature have used hHl. Representative currents for the four variants and hHl are shown in Fig. 3. For those variants that expressed robust current, no significant differences were identified in i) the parameters of activation (Fig. 4A, Table 3), ii) current decay (Table 3), iii) recovery from inactivation (Fig. 4C, Table 3) and iv) late or persistent currents (Table 3). The midpoint of inactivation for hHl, however, was significantly negative to the two variants lacking Q1077 [Q1077del] and [H558R;Q1077del] (Fig. 4B and Table 3).

Table 3. Voltage-dependent Kinetic Parameters for hNa_v1.5 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
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: $I_{Na}(t) = 1 - (A_f * \exp^{-t/\tau_f} + A_s * \exp^{-t/\tau_s}) + \text{offset}$ 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].

[0062] 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 β1 subunit increased current density when co-expressed with the α subunit of Nav1.5 (Nuss, HB et al., *J. Gen. Physiol.* 106:1171-1191, 1995). The β1 subunit also “rescued” the trafficking defective SCN5A mutations (Valdivia, CR 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 α 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 $\beta 1$ subunit. We were unable to significantly increase endogenous currents in untransfected cells by co-transfection with $\beta 1$ (1.0 ± 0.5 pA/pF, $n=9$), incubation with mexiletine 100 μ M 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;Q1077del] were co-expressed (plasmid DNA 0.75 μ g 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.

[0063] *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. 6A). The [Q 1077del] variant that gave robust current densities showed a rim of fluorescence at the cell surface as expected for a normally trafficking channel (Fig. 6B). The [H558R] variant expressed almost no current, but also showed fluorescence at the cell surface (Fig. 6C) suggesting that the lack of current was not caused by a trafficking defect.

[0064] 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 (Fig. 6D & E). We had previously shown M1766L to be trafficking defective in hH1a [T559A;Q1077del;M1766L] but to be normally trafficking in hH1b [H558R;L6181;Q1077del;M1766L] (Ye, B. et al., *Physiol. Genomics* 12:187-193, 2003). When the M1766L mutation was put into [Q1077del] to make [Q1077del;M1766L] (Fig. 6D), 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. 6D, and the fourth image in Fig. 6D 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;Q1077del] background, the channel is rescued and makes it to the cell periphery (Fig. 6E), consistent with previous data and also showing that the rare variant L6181 in hH1b was not responsible for “rescuing” the trafficking defect.

CLAIMS

WE CLAIM:

1. An isolated nucleic acid comprising a polynucleotide selected from the group consisting of:
 - (1) a first polynucleotide that encodes a polypeptide selected from the group consisting of
 - (i) an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively,
 - (ii) an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively,
 - (iii) an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and
 - (iv) an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted,
 - (2) a second polynucleotide that is at least 80% identical to the first polynucleotide over the entire length of the first polypeptide,
 - (3) a third polynucleotide that encodes any of the SCN5A polypeptides with a conservative substitution, deletion or rearrangement at one or more non-critical amino acid position, and
 - (4) a fourth polynucleotide that is a complement of the first, second or third polynucleotide.
2. The isolated nucleic acid of claim 1, wherein the nucleic acid comprises a polynucleotide selected from the group consisting of the first polynucleotide, the second polynucleotide and a polynucleotide that is a complement of the first or second polynucleotide.
3. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 1991 amino acid positions other than positions 558, 559, 618, 1027 and 1077.

4. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 2001 amino acid positions other than positions 558, 559, 618, 1027 and 1077.
5. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 2006 amino acid positions other than positions 558, 559, 618, 1027 and 1077.
6. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide that is identical to SEQ ID NO:2 at at least 2010 amino acid positions other than positions 558, 559, 618, 1027 and 1077.
7. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively.
8. The isolated nucleic acid of claim 7, wherein the first polynucleotide encodes SEQ ID NO:2.
9. The isolated nucleic acid of claim 8, wherein the first polynucleotide is nucleotides 1 to 6048 of SEQ ID NO:1.
10. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively.
11. The isolated nucleic acid of claim 10, wherein the first polynucleotide encodes SEQ ID NO:4.
12. The isolated nucleic acid of claim 11, wherein the first polynucleotide is nucleotides 1 to 6048 of SEQ ID NO:3.

13. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted.
14. The isolated nucleic acid of claim 13, wherein the first polynucleotide encodes SEQ ID NO:6.
15. The isolated nucleic acid of claim 14, wherein the first polynucleotide is nucleotides 1 to 6045 of SEQ ID NO:5.
16. The isolated nucleic acid of claim 1, wherein the first polynucleotide encodes an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted.
17. The isolated nucleic acid of claim 16, wherein the first polynucleotide encodes SEQ ID NO:8.
18. The isolated nucleic acid of claim 17, wherein the first polynucleotide is nucleotides 1 to 6045 of SEQ ID NO:7.
19. A genetic construct comprising the polynucleotide of claim 1 operably linked to a non-native expression control sequence.

20. A cell comprising a polynucleotide selected from the group consisting of (1) a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (2) a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (3) a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and (4) a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, wherein each polynucleotide is operably linked to a non-native expression control sequence.

21. The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, and wherein the polynucleotide is operably linked to a non-native expression control sequence.

22. The cell of claim 21, wherein the polynucleotide encodes SEQ ID NO:2.

23. The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, and wherein the polynucleotide is operably linked to a non-native expression control sequence.

24. The cell of claim 23, wherein the polynucleotide encodes SEQ ID NO:4.

25. The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and wherein the polynucleotide is operably linked to a non-native expression control sequence.

26. The cell of claim 25, wherein the polynucleotide encodes SEQ ID NO:6.

27. The cell of claim 20, wherein the cell comprises a polynucleotide that encodes an SCN5A polypeptide having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, wherein the polynucleotide is operably linked to a non-native expression control sequence.

28. The cell of claim 27, wherein the polynucleotide encodes SEQ ID NO:8.

29. The cell of claim 20, wherein the cell is from a human embryonic kidney cell line.

30. An isolated polypeptide comprising an amino acid sequence encoded by the first or third polynucleotide of claim 1.

31. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide of claim 1.

32. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 3.

33. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 4.

34. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 5.

35. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 6.

36. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 7.

37. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 8.

38. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 10.

39. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 11.

40. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 13.

41. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 14.

42. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 16.

43. An isolated polypeptide comprising an amino acid sequence encoded by the first polynucleotide in claim 17.

44. An antibody that binds specifically to a polypeptide of claim 31.

45. A method for identifying an agent that can alter the activity of a sodium channel, the method comprising the steps of:
 providing a cultured cell according to claim 20;
 exposing the cell to a test agent;
 determining sodium channel activity of the cell; and
 comparing the sodium channel activity to that of a control cell that is not exposed to the test agent wherein a difference in sodium channel activity indicates that the agent can alter the activity of the sodium channel.

46. The method of claim 45, wherein the determining step comprises measuring a parameter selected from the group consisting of a sodium current across a cellular membrane, a membrane potential, and an intracellular sodium level.

47. A method for identifying an agent that can alter the expression of a sodium channel, the method comprising the steps of:

exposing a cell that contains a first polynucleotide in claim 1 to a test agent wherein the expression of the polynucleotide is under the control of its native control sequences; determining the expression level of the polynucleotide at the mRNA or protein level; and

comparing the expression level to that of a control cell that is not exposed to the test agent wherein a difference in expression level indicates that the agent can alter the expression of the sodium channel.

48. A method for determining whether a biological sample or a preparation derived from the biological sample contains a polypeptide of claim 32 or a nucleic acid encoding the polypeptide, the method comprising the steps of:

contacting the sample or preparation with a polynucleotide probe, a pair of polynucleotide primers or an antibody specific for the nucleic acid or polypeptide; and

determining whether the probe or antibody specifically binds to a component in the sample or preparation, or the primers specifically amplify a component of the sample, said binding or amplification being an indication that the sample contains the nucleic acid or polypeptide.

49. A method for determining whether a mutation on a sodium channel is associated with a disease comprising the step of:

introducing the mutation into the first polynucleotide of claim 1; and

determining the effect of the mutation in a suitable model for the disease.

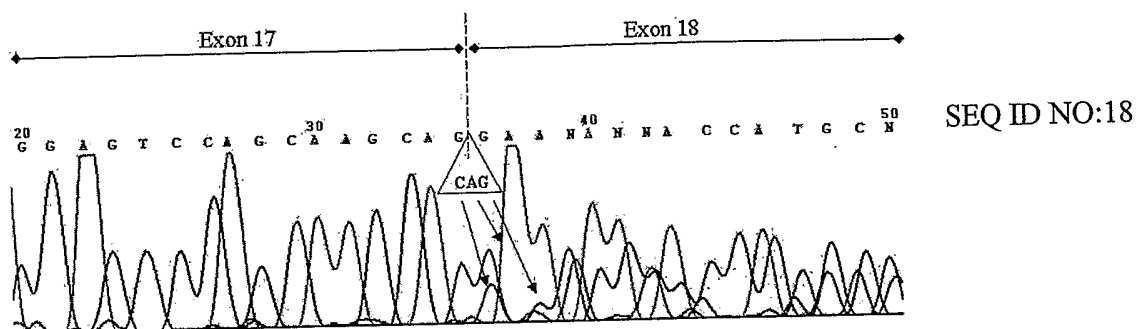
50. A method for determining whether a human or non-human subject is at risk for Long QT syndrome, the method comprising the step of:

determining whether the subject carries an M1766L mutation on an SCN5A variant selected from the group consisting of (1) a variant having a histidine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (2) a variant having an arginine, threonine, leucine, arginine and glutamine at amino acid positions 558, 559, 618, 1027 and 1077, respectively, (3) a variant having a histidine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted, and (4) a variant having an arginine, threonine, leucine and arginine at amino acid positions 558, 559, 618 and 1027, respectively, with the amino acid at amino acid position 1077 deleted,

wherein an M1766L mutation on a (1), (2) or (3) variant indicates that the subject is at risk for Long QT syndrome, and wherein an M1766L mutation on a (4) variant indicates that the subject is not at risk for Long QT syndrome.

Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS
 Inventor: Jonathan C. Makielski, Bin Ye, Michael J. Ackerman
 Docket Number: 960296.98989

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mRNA (Alternative Splicing)

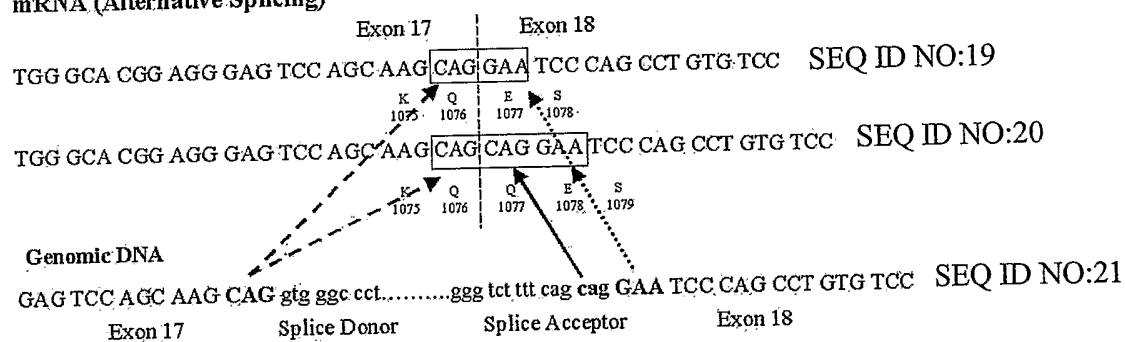


FIG. 1

Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS
Inventor: Jonathan C. Makielski, Bin Ye, Michael J. Ackerman
Docket Number: 960296.98989

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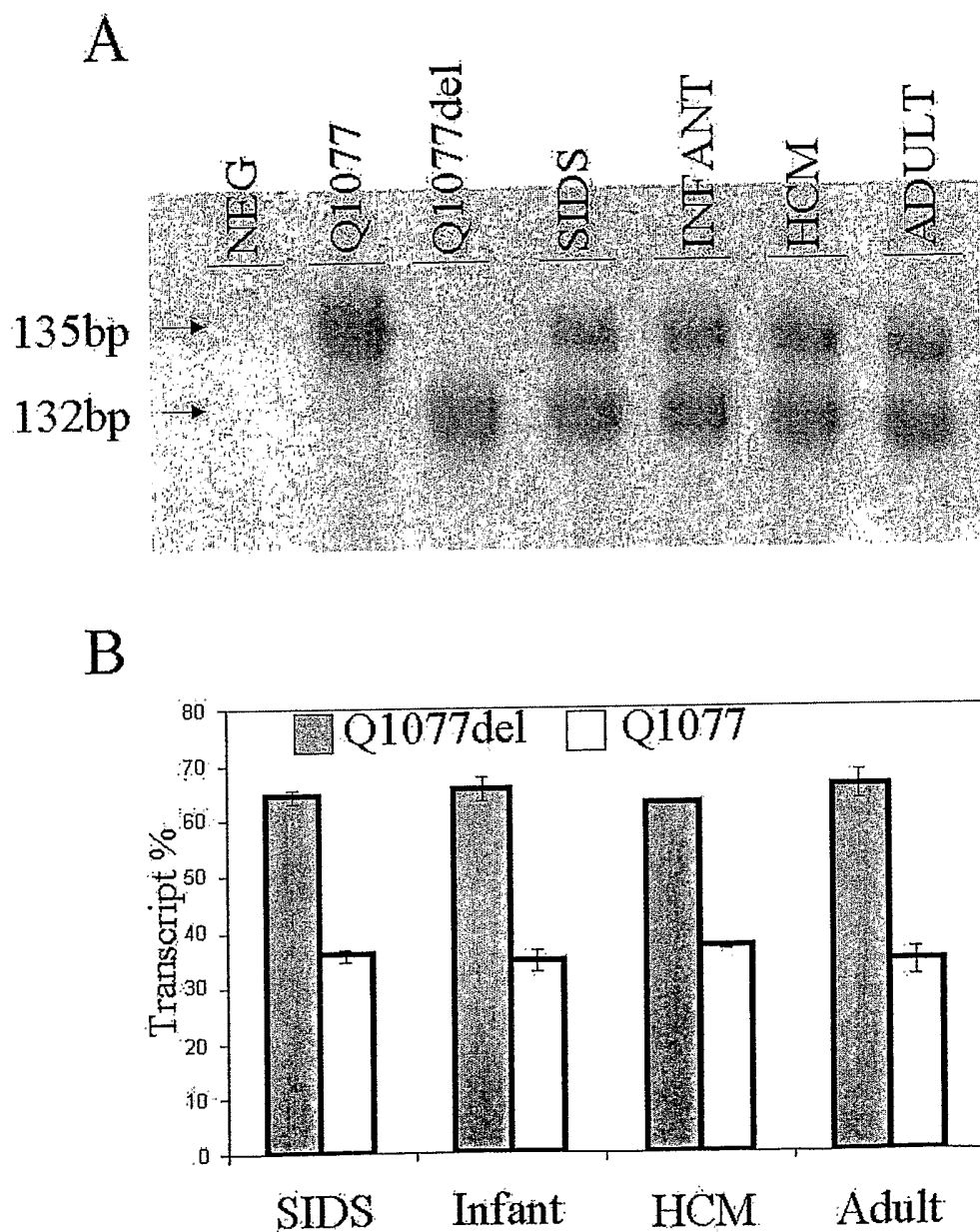


FIG. 2

Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS
Inventor: Jonathan C. Makielski, Bin Ye, Michael J. Ackerman
Docket Number: 960296.98989

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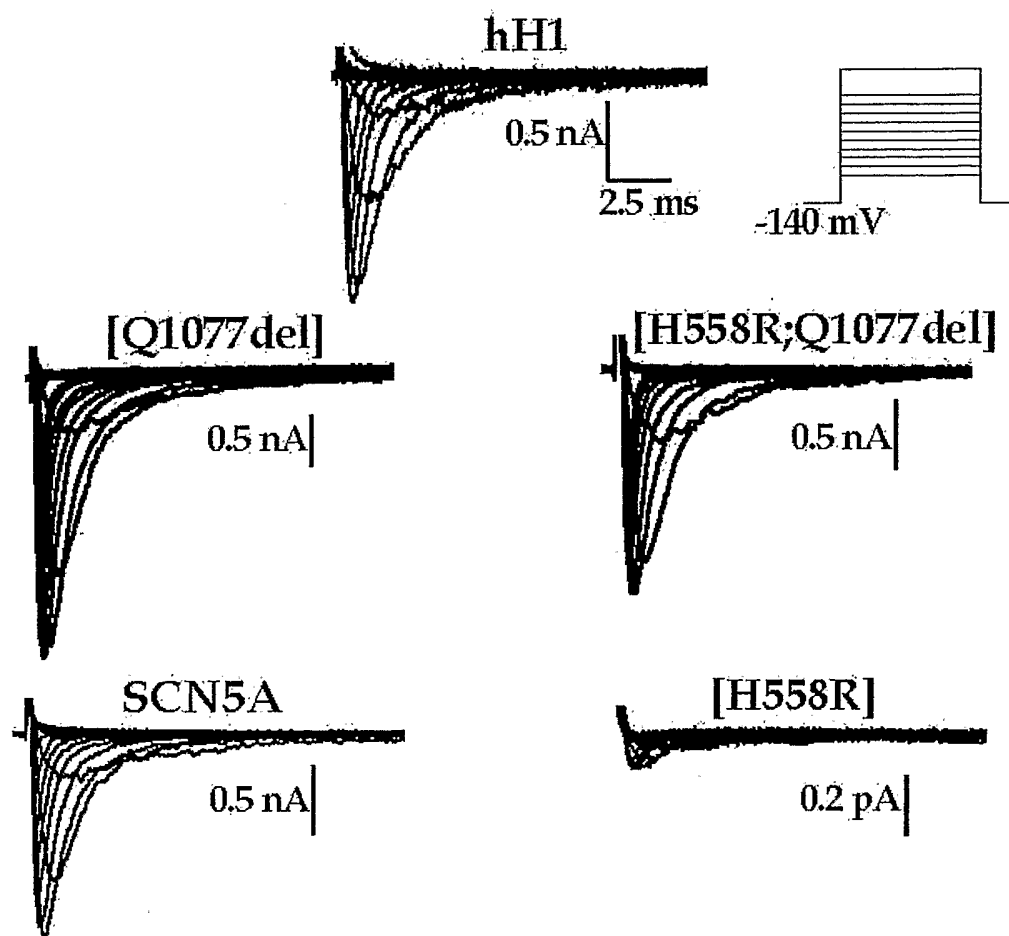


FIG. 3

Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS
Inventor: Jonathan C. Makielski, Bin Ye, Michael J. Ackerman
Docket Number: 960296.98989

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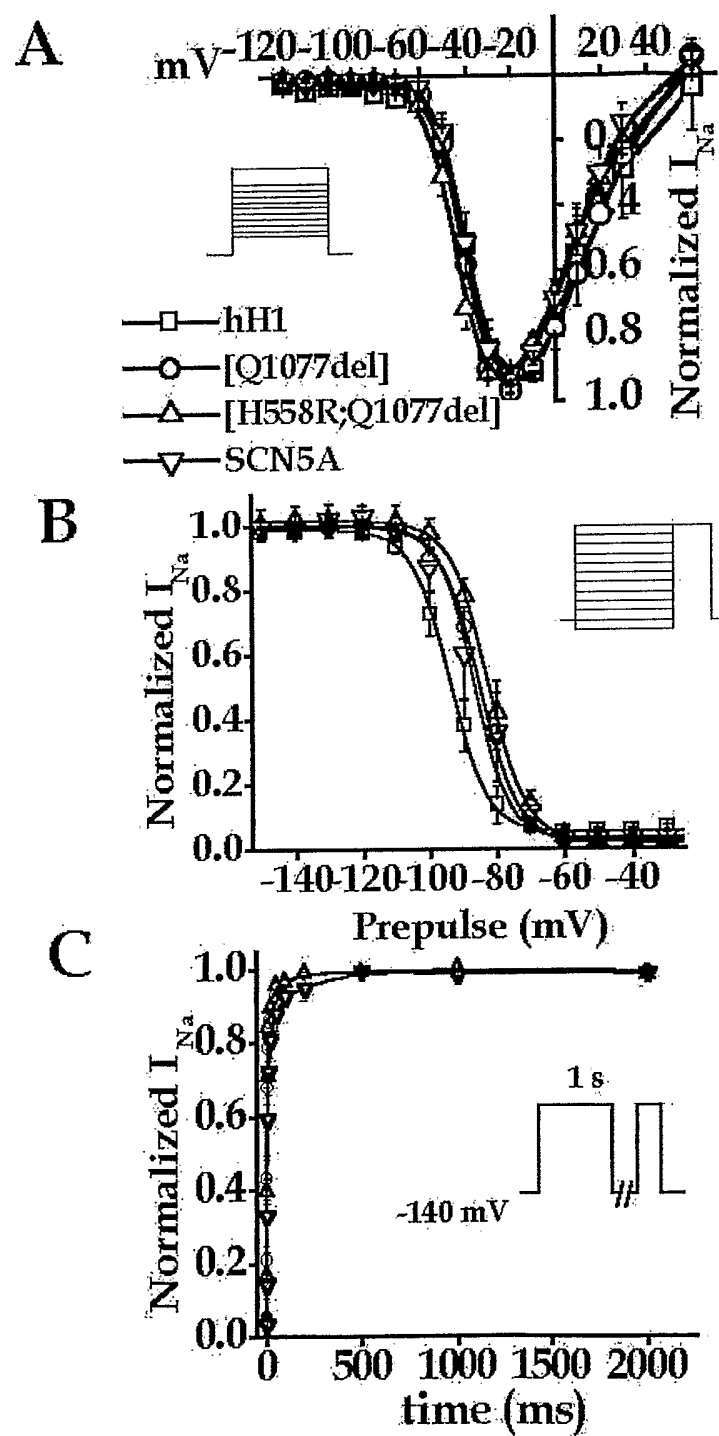


FIG. 4

Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS
Inventor: Jonathan C. Makielski, Bin Ye, Michael J. Ackerman
Docket Number: 960296.98989

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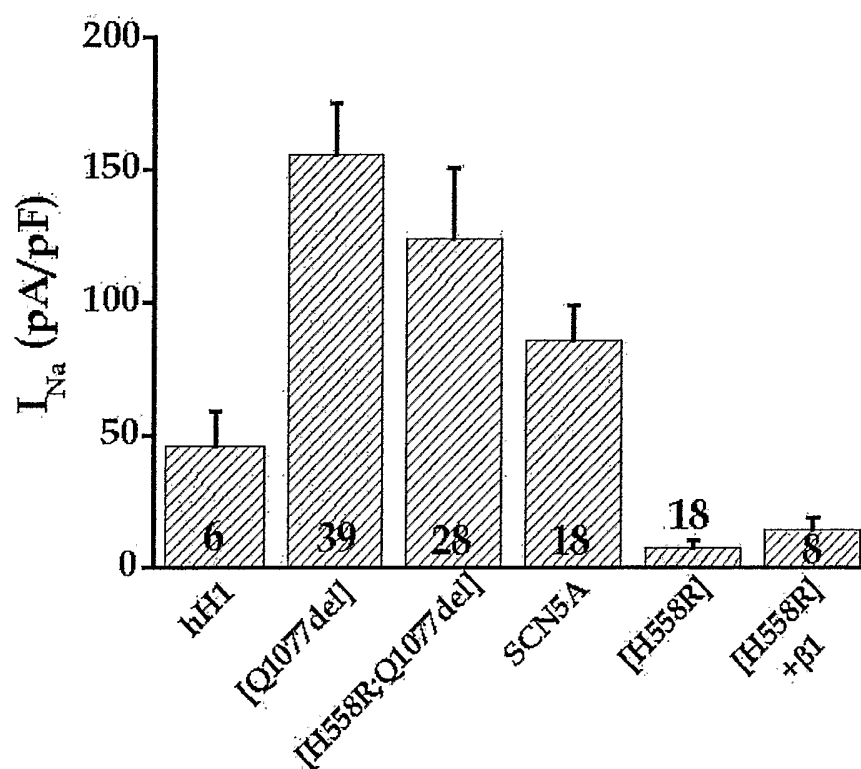


FIG. 5

Title: SODIUM CHANNEL ALPHA SUBUNIT VARIANTS
 Inventor: Jonathan C. Makielski, Bin Ye, Michael J. Ackerman
 Docket Number: 960296.98989

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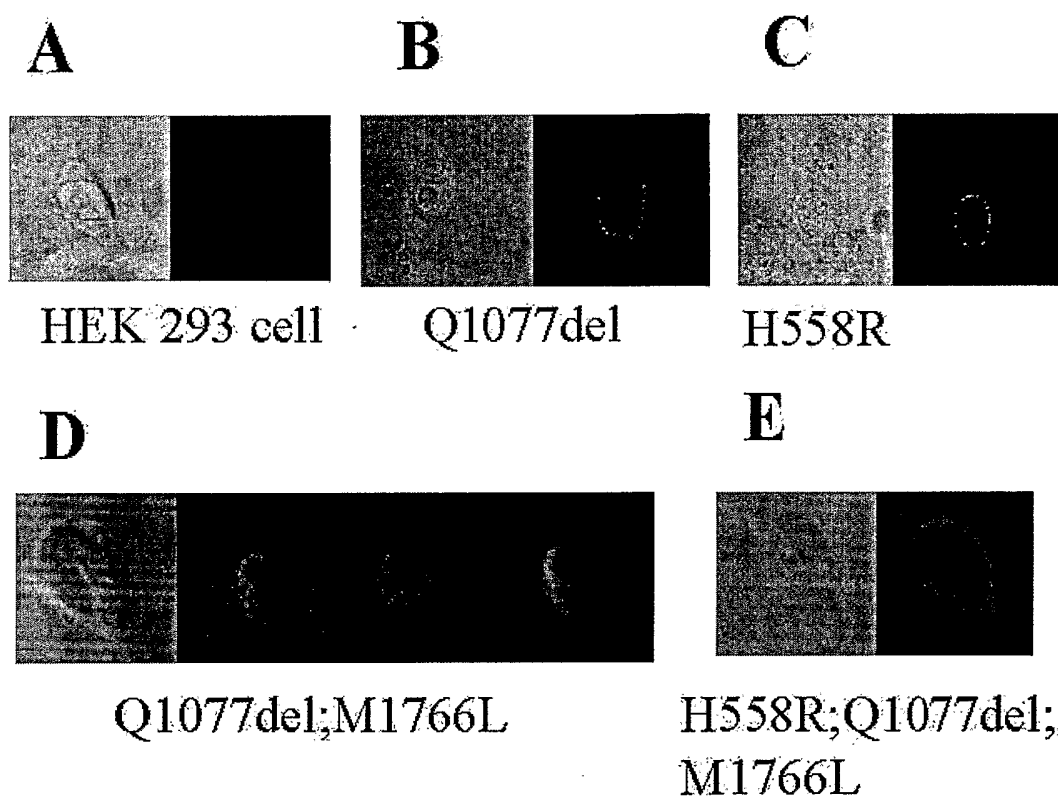


FIG. 6

SEQUENCE LISTING

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Ye, Bin
Ackerman, Michael J.

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Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln	
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Ala Arg Gly Ser Thr Thr Leu Gln Glu Ser Arg Glu Gly Leu Pro Glu	
35 40 45	
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Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr	
100 105 110	
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Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu	
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Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu				
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Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser				
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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	
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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	
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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	
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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	
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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	
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Tyr Ser Pro Pro Pro Pro Glu Thr Glu Lys Val Pro Pro Thr Arg	
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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	
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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	
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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	
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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	
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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	
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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	
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Gln Asp Val Lys Asp Pro Glu Asp Cys Phe Thr Glu Gly Cys Val	
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Arg Arg Cys Pro Cys Cys Ala Val Asp Thr Thr Gln Ala Pro Gly	
1175 1180 1185	
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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	
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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	
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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	
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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	
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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	
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Gly Asp Leu Pro Leu Asn Tyr Thr Ile Val Asn Asn Lys Ser Gln	

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Cys Glu Ser Leu Asn Leu Thr	Gly Glu Leu Tyr Trp	Thr Lys Val	
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Lys Val Asn Phe Asp Asn Val	Gly Ala Gly Tyr Leu	Ala Leu Leu	
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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	
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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	
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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	
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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	
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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	
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Lys Lys Pro Gln Lys Pro Ile	Pro Arg Pro Leu Asn	Lys Tyr Gln	
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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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Ile Met Phe Leu Ile Cys Leu	Asn Met Val Thr Met	Met Val Glu	
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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	
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Asn Leu Leu Phe Val Ala Ile	Phe Thr Gly Glu Cys	Ile Val Lys	
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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	
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Phe Asp Phe Val Val Val Ile	Leu Ser Ile Val Gly	Thr Val Leu	
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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		
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Val	Ile	Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Arg		
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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		
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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		
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Trp	Glu	Ala	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Gln	Thr	Phe	Ala		
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Asn	Ser	Met	Leu	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp		
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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		
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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		
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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		
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Asn	Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Thr	Glu	Pro	Leu	Ser	Glu		
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Asp	Asp	Phe	Asp	Met	Phe	Tyr	Glu	Ile	Trp	Glu	Lys	Phe	Asp	Pro		
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Glu	Ala	Thr	Gln	Phe	Ile	Glu	Tyr	Ser	Val	Leu	Ser	Asp	Phe	Ala		
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Asp	Ala	Leu	Ser	Glu	Pro	Leu	Arg	Ile	Ala	Lys	Pro	Asn	Gln	Ile		
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Ser	Leu	Ile	Asn	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile		
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His Cys Met Asp Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly	
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Glu Ser Gly Glu Met Asp Ala Leu Lys Ile Gln Met Glu Glu Lys	
1865 1870 1875	
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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	
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Gln Arg Ala Phe Arg Arg His Leu Leu Gln Arg Ser Leu Lys His	
1910 1915 1920	
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Ala Ser Phe Leu Phe Arg Gln Gln Ala Gly Ser Gly Leu Ser Glu	
1925 1930 1935	
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Glu Asp Ala Pro Glu Arg Glu Gly Leu Ile Ala Tyr Val Met Ser	
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Glu Asn Phe Ser Arg Pro Leu Gly Pro Pro Ser Ser Ser Ser Ile	
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Thr Ser Asp Asn Leu Gln Val Arg Gly Ser Asp Tyr Ser His Ser	
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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
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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
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Glu Gly Tyr Arg Cys Leu Lys Ala Gly Glu Asn Pro Asp His Gly Tyr
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Thr Ser Phe Asp Ser Phe Ala Trp Ala Phe Leu Ala Leu Phe Arg Leu
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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
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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
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Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
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Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
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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
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Asp Asp Glu Asn Ser Thr Ala Gly Glu Ser Glu Ser His His Thr Ser
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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
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Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp
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Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu
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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 Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln 900 905 910	2736
tca tta tgc ctg ctg gtc ttc ttg ctt gtt atg gtc att ggc aac ctt Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu 915 920 925	2784
gtg gtc ctg aat ctc ttc ctg gcc ttg ctg ctc agc tcc ttc agt gca Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala 930 935 940	2832
gac aac ctc aca gcc cct gat gag gac aga gag atg aac aac ctc cag Asp Asn Leu Thr Ala Pro Asp Glu Asp Arg Glu Met Asn Asn Leu Gln 945 950 955 960	2880
ctg gcc ctg gcc cgc atc cag agg ggc ctg cgc ttt gtc aag cgg acc Leu Ala Leu Ala Arg Ile Gln Arg Gly Leu Arg Phe Val Lys Arg Thr 965 970 975	2928
acc tgg gat ttc tgc tgt ggt ctc ctg cgg cag cgg cct cag aag ccc Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro 980 985 990	2976
gca gcc ctt gcc gcc cag ggc cag ctg ccc agc tgc att gcc acc ccc Ala Ala Leu Ala Ala Gln Gly Gln Leu Pro Ser Cys Ile Ala Thr Pro 995 1000 1005	3024
tac tcc ccg cca ccc cca gag acg gag aag gtg cct ccc acc cgc Tyr Ser Pro Pro Pro Pro Glu Thr Glu Lys Val Pro Pro Thr Arg 1010 1015 1020	3069
aag gaa aca cgg ttt gag gaa ggc gag caa cca ggc cag ggc acc Lys Glu Thr Arg Phe Glu Glu Gly Glu Gln Pro Gly Gln Gly Thr 1025 1030 1035	3114
ccc ggg gat cca gag ccc gtg tgt gtg ccc atc gct gtg gcc gag Pro Gly Asp Pro Glu Pro Val Cys Val Pro Ile Ala Val Ala Glu 1040 1045 1050	3159
tca gac aca gat gac caa gaa gaa gat gag gag aac agc ctg ggc Ser Asp Thr Asp Asp Gln Glu Glu Asp Glu Glu Asn Ser Leu Gly 1055 1060 1065	3204
acg gag gag gag tcc agc aag cag cag gaa tcc cag cct gtg tcc Thr Glu Glu Glu Ser Ser Lys Gln Gln Glu Ser Gln Pro Val Ser 1070 1075 1080	3249
ggt ggc cca gag gcc cct ccg gat tcc agg acc tgg agc cag gtg Gly Gly Pro Glu Ala Pro Pro Asp Ser Arg Thr Trp Ser Gln Val 1085 1090 1095	3294
tca gcg act gcc tcc tct gag gcc gag gcc agt gca tct cag gcc Ser Ala Thr Ala Ser Ser Glu Ala Glu Ala Ser Ala Ser Gln Ala 1100 1105 1110	3339
gac tgg cgg cag cag tgg aaa gcg gaa ccc cag gcc cca ggg tgc Asp Trp Arg Gln Gln Trp Lys Ala Glu Pro Gln Ala Pro Gly Cys 1115 1120 1125	3384
ggt gag acc cca gag gac agt tgc tcc gag ggc agc aca gca gac Gly Glu Thr Pro Glu Asp Ser Cys Ser Glu Gly Ser Thr Ala Asp 1130 1135 1140	3429

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Met Thr Asn Thr Ala Glu Leu Leu Glu Gln Ile Pro Asp Leu Gly	
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Gln Asp Val Lys Asp Pro Glu Asp Cys Phe Thr Glu Gly Cys Val	
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His Ser Trp Phe Glu Thr Phe Ile Ile Phe Met Ile Leu Leu Ser	
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Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Leu Glu Glu Arg Lys	
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Thr Ile Lys Val Leu Leu Glu Tyr Ala Asp Lys Met Phe Thr Tyr	
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Val Phe Val Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Phe	
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Lys Lys Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile	
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Val Asp Val Ser Leu Val Ser Leu Val Ala Asn Thr Leu Gly Phe	
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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	
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Val Asn Ala Leu Val Gly Ala Ile Pro Ser Ile Met Asn Val Leu	
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Asn Leu Phe Ala Gly Lys Phe Gly Arg Cys Ile Asn Gln Thr Glu	
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Gly Asp Leu Pro Leu Asn Tyr Thr Ile Val Asn Asn Lys Ser Gln	

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Cys Glu Ser Leu Asn Leu Thr	Gly Glu Leu Tyr Trp	Thr Lys Val	
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Lys Val Asn Phe Asp Asn Val	Gly Ala Gly Tyr Leu	Ala Leu Leu	
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Gln Val Ala Thr Phe Lys Gly	Trp Met Asp Ile Met	Tyr Ala Ala	
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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	
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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	
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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	
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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	
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Lys Lys Pro Gln Lys Pro Ile	Pro Arg Pro Leu Asn	Lys Tyr Gln	
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Gly Phe Ile Phe Asp Ile Val	Thr Lys Gln Ala Phe	Asp Val Thr	
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Ile Met Phe Leu Ile Cys Leu	Asn Met Val Thr Met	Met Val Glu	
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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	
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Asn Leu Leu Phe Val Ala Ile	Phe Thr Gly Glu Cys	Ile Val Lys	
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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	
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Phe Asp Phe Val Val Val Ile	Leu Ser Ile Val Gly	Thr Val Leu	
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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		
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Val	Ile	Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Arg		
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Gly	Ala	Lys	Gly	Ile	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser		
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Trp	Glu	Ala	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Gln	Thr	Phe	Ala		
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Asp	Gly	Leu	Leu	Ser	Pro	Ile	Leu	Asn	Thr	Gly	Pro	Pro	Tyr	Cys		
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Asp	Pro	Thr	Leu	Pro	Asn	Ser	Asn	Gly	Ser	Arg	Gly	Asp	Cys	Gly		
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Ser	Pro	Ala	Val	Gly	Ile	Leu	Phe	Phe	Thr	Thr	Tyr	Ile	Ile	Ile		
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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		
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Asn	Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Thr	Glu	Pro	Leu	Ser	Glu		
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Asp	Asp	Phe	Asp	Met	Phe	Tyr	Glu	Ile	Trp	Glu	Lys	Phe	Asp	Pro		
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Glu	Ala	Thr	Gln	Phe	Ile	Glu	Tyr	Ser	Val	Leu	Ser	Asp	Phe	Ala		
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Asp	Ala	Leu	Ser	Glu	Pro	Leu	Arg	Ile	Ala	Lys	Pro	Asn	Gln	Ile		
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Ser	Leu	Ile	Asn	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile		
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His Cys Met Asp Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly	
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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	
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Glu Asp Ala Pro Glu Arg Glu Gly Leu Ile Ala Tyr Val Met Ser	
1940 1945 1950	
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Glu Asn Phe Ser Arg Pro Leu Gly Pro Pro Ser Ser Ser Ser Ile	
1955 1960 1965	
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Ser Ser Thr Ser Phe Pro Pro Ser Tyr Asp Ser Val Thr Arg Ala	
1970 1975 1980	
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Thr Ser Asp Asn Leu Gln Val Arg Gly Ser Asp Tyr Ser His Ser	
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Glu Asp Leu Ala Asp Phe Pro Pro Ser Pro Asp Arg Asp Arg Glu	
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Ser Ile Val	
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<211> 2016

<212> PRT

<213> Homo sapiens

<400> 4

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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
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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
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Thr Val Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe
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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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Ser Asp Val Leu Leu Cys Gly Asn Ser Ser Asp Ala Gly Thr Cys Pro
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Met Thr Gln Asp Cys Trp Glu Arg Leu Tyr Gln Gln Thr Leu Arg Ser
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Ala Gly Lys Ile Tyr Met Ile Phe Phe Met Leu Val Ile Phe Leu Gly
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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
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Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu
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Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Leu Glu Met Ser
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Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys
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Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys
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Ser Asp Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr
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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
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 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
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Leu Thr Ile Thr Met Cys Ile Val Leu Asn Thr Leu Phe Met Ala Leu
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Glu His Tyr Asn Met Thr Ser Glu Phe Glu Glu Met Leu Gln Val Gly
 740 745 750

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Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe
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Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile
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Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His
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Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys
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Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met Glu Val Ser Gly Gln
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Ser Leu Cys Leu Leu Val Phe Leu Leu Val Met Val Ile Gly Asn Leu
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Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro
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 995 1000 1005

Tyr Ser Pro Pro Pro Pro Glu Thr Glu Lys Val Pro Pro Thr Arg
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1925						1930					1935			
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1970 1975 1980

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Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln
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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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Pro Asp Leu Tyr Gly Asn Pro Pro Gln Glu Leu Ile Gly Glu Pro Leu
65 70 75 80
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Glu Asp Leu Asp Pro Phe Tyr Ser Thr Gln Lys Thr Phe Ile Val Leu
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Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
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Ser Phe Tyr Leu Val Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr				
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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				
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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				
	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				
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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				
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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				
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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				
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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				
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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				
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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				
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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				
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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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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	
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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	
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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	
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Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe	770	775	780	
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Asp Ser Ile Ile Val Ile Leu Ser Leu Met Glu Leu Gly Leu Ser Arg	785	790	795	800
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Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe	805	810	815	
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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	
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Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn	850	855	860	
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Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His	865	870	875	880
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Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys	885	890	895	

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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	
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Lys Glu Thr Arg Phe Glu Glu Gly Glu Gln Pro Gly Gln Gly Thr	
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Arg Cys	Pro Cys	Cys Ala	Val	Asp Thr	Thr Gln	Ala	Pro Gly	Lys	
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Ser Trp	Phe Glu	Thr Phe	Ile	Ile Phe	Met Ile	Leu	Leu Ser	Ser	
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Gly Ala	Leu Ala	Phe Glu	Asp	Ile Tyr	Leu Glu	Glu	Arg Lys	Thr	
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Ile Lys	Val Leu	Leu Glu	Tyr	Ala Asp	Lys Met	Phe	Thr Tyr	Val	
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Phe Val	Leu Glu	Met Leu	Leu	Lys Trp	Val Ala	Tyr	Gly Phe	Lys	
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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	ggc 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 Gly	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	ggg 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
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 gcc cgc atc ctc aga ctg atc cga ggg Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg Leu Ile Arg Gly 1625 1630 1635	4914
gcc aag ggg atc cgc acg ctg ctc ttt gcc ctc atg atg tcc ctg Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met Met Ser Leu 1640 1645 1650	4959
cct gcc ctc ttc aac atc ggg ctg ctg ctc ttc ctc gtc atg ttc Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val Met Phe 1655 1660 1665	5004
atc tac tcc atc ttt gcc atg gcc aac ttc gct tat gtc aag tgg Ile Tyr Ser Ile Phe Gly Met Ala Asn Phe Ala Tyr Val Lys Trp 1670 1675 1680	5049
gag gct ggc atc gac gac atg ttc aac ttc cag acc ttc gcc aac Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Gln Thr Phe Ala Asn 1685 1690 1695	5094
agc atg ctg tgc ctc ttc cag atc acc acg tcg gcc ggc tgg gat Ser Met Leu Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp 1700 1705 1710	5139
ggc ctc ctc agc ccc atc ctc aac act ggg ccg ccc tac tgc gac Gly Leu Leu Ser Pro Ile Leu Asn Thr Gly Pro Pro Tyr Cys Asp 1715 1720 1725	5184
ccc act ctg ccc aac agc aat ggc tct cgg ggg gac tgc ggg agc Pro Thr Leu Pro Asn Ser Asn Gly Ser Arg Gly Asp Cys Gly Ser 1730 1735 1740	5229
cca gcc gtg ggc atc ctc ttc ttc acc acc tac atc atc atc tcc Pro Ala Val Gly Ile Leu Phe Phe Thr Thr Tyr Ile Ile Ile Ser 1745 1750 1755	5274
ttc ctc atc gtg gtc aac atg tac att gcc atc atc ctg gag aac Phe Leu Ile Val Val Asn Met Tyr Ile Ala Ile Ile Leu Glu Asn 1760 1765 1770	5319
ttc agc gtg gcc acg gag gag agc acc gag ccc ctg agt gag gac Phe Ser Val Ala Thr Glu Glu Ser Thr Glu Pro Leu Ser Glu Asp 1775 1780 1785	5364
gac ttc gat atg ttc tat gag atc tgg gag aaa ttt gac cca gag Asp Phe Asp Met Phe Tyr Glu Ile Trp Glu Lys Phe Asp Pro Glu 1790 1795 1800	5409
gcc act cag ttt att gag tat tcg gtc ctg tct gac ttt gcc gat Ala Thr Gln Phe Ile Glu Tyr Ser Val Leu Ser Asp Phe Ala Asp 1805 1810 1815	5454
gcc ctg tct gag cca ctc cgt atc gcc aag ccc aac cag ata agc Ala Leu Ser Glu Pro Leu Arg Ile Ala Lys Pro Asn Gln Ile Ser 1820 1825 1830	5499
ctc atc aac atg gac ctg ccc atg gtg agt ggg gac cgc atc cat Leu Ile Asn Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His 1835 1840 1845	5544

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 cctttttcac	6095
Ile Val	
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taagaaatgg gcct	6169

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<211> 2015

<212> PRT

<213> Homo sapiens

<400> 6

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 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

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	
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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

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
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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
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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

Glu Ser Leu Asn Leu Thr Gly Glu Leu Tyr Trp Thr Lys Val Lys
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Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala Leu Leu Gln
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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		
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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		
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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		
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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
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
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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	

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1970 1975 1980

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Ile Val
2015

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Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Met Ala Glu Lys Gln
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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
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Asn Lys Gly Lys Thr Ile Phe Arg Phe Ser Ala Thr Asn Ala Leu Tyr
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Val Leu Ser Pro Phe His Pro Ile Arg Arg Ala Ala Val Lys Ile Leu
115 120 125
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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	
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Leu Ala Arg Gly Phe Cys Leu His Ala Phe Thr Phe Leu Arg Asp Pro	
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Trp Asn Trp Leu Asp Phe Ser Val Ile Ile Met Ala Tyr Thr Thr Glu	
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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	
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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				
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Arg Phe Gln Glu Ala Met Glu Met Leu Lys Lys Glu His Glu Ala Leu				
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Thr Ile Arg Gly Val Asp Thr Val Ser Arg Ser Ser Ser Leu Glu Met Ser				
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Pro Leu Ala Pro Val Asn Ser His Glu Arg Arg Ser Lys Arg Arg Lys				
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Arg Met Ser Ser Gly Thr Glu Glu Cys Gly Glu Asp Arg Leu Pro Lys				
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Ser Asp Ser Ser Glu Asp Gly Pro Arg Ala Met Asn His Leu Ser Leu Thr				
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Arg Gly Leu Ser Arg Thr Ser Met Lys Pro Arg Ser Ser Ser Arg Gly Ser				
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Leu Leu Val Pro Trp Pro Leu Arg Arg Thr Ser Ala Gln Gly Gln Pro				
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Ser Pro Gly Thr Ser Ala Pro Gly His Ala Leu His Gly Lys Lys Asn				
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Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Leu Gly Ala Gly Asp				
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Pro Glu Ala Thr Ser Pro Gly Ser His Leu Leu Arg Pro Val Met Leu				
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cag atg ctg acc tcc cag gct ccg tgt gta gat ggc ttc gag gag cca				1968

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Ile Ala Leu Asp Pro Tyr Tyr Tyr Phe Gln Gln Gly Trp Asn Ile Phe	
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Met Ser Asn Leu Ser Val Leu Arg Ser Phe Arg Leu Leu Arg Val Phe	
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Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Thr Leu Ile Lys Ile Ile	
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Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Asn	
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Tyr Ser Glu Leu Arg Asp Ser Asp Ser Gly Leu Leu Pro Arg Trp His	
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Met Met Asp Phe Phe His Ala Phe Leu Ile Ile Phe Arg Ile Leu Cys	
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acc tgg gat ttc tgc tgt ggt ctc ctg cgg cag cgg cct cag aag ccc Thr Trp Asp Phe Cys Cys Gly Leu Leu Arg Gln Arg Pro Gln Lys Pro 980 985 990	2976
gca gcc ctt gcc gcc cag ggc cag ctg ccc agc tgc att gcc acc ccc Ala Ala Leu Ala Ala Gln Gly Gln Leu Pro Ser Cys Ile Ala Thr Pro 995 1000 1005	3024
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Asp Val	Lys Asp	Pro Glu	Asp	Cys Phe	Thr Glu	Gly	Cys Val	Arg	
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Arg Cys	Pro Cys	Cys Ala	Val	Asp Thr	Thr Gln	Ala	Pro Gly	Lys	
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Val Trp	Trp Arg	Leu Arg	Lys	Thr Cys	Tyr His	Ile	Val Glu	His	
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Ser Trp	Phe Glu	Thr Phe	Ile	Ile Phe	Met Ile	Leu	Leu Ser	Ser	
1205			1210			1215			
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Gly Ala	Leu Ala	Phe Glu	Asp	Ile Tyr	Leu Glu	Glu	Arg Lys	Thr	
1220			1225			1230			
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Ile Lys	Val Leu	Leu Glu	Tyr	Ala Asp	Lys Met	Phe	Thr Tyr	Val	
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Phe Val	Leu Glu	Met Leu	Leu	Lys Trp	Val Ala	Tyr	Gly Phe	Lys	
1250			1255			1260			
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Lys Tyr	Phe Thr	Asn Ala	Trp	Cys Trp	Leu Asp	Phe	Leu Ile	Val	
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Asp Val	Ser Leu	Val Ser	Leu	Val Ala	Asn Thr	Leu	Gly Phe	Ala	
1280			1285			1290			
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Glu Met	Gly Pro	Ile Lys	Ser	Leu Arg	Thr Leu	Arg	Ala Leu	Arg	
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Pro Leu	Arg Ala	Leu Ser	Arg	Phe Glu	Gly Met	Arg	Val Val	Val	
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Asn Ala	Leu Val	Gly Ala	Ile	Pro Ser	Ile Met	Asn	Val Leu	Leu	
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Leu Phe	Ala Gly	Lys Phe	Gly	Arg Cys	Ile Asn	Gln	Thr Glu	Gly	
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Asp Leu	Pro Leu	Asn Tyr	Thr	Ile Val	Asn Asn	Lys	Ser Gln	Cys	

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ctg ctc ttt gtg gcc atc Leu Leu Phe Val Ala Ile 1565	ttc aca ggc gag tgt Phe Thr Asn Ser Trp 1570	att gtc aag ctg Ile Val Lys Leu 1575	4734
gct gcc ctg cgc cac tac Ala Ala Leu Arg His Tyr 1580	tac ttc acc aac agc Tyr Phe Thr Asn Ser 1585	tgg aat atc ttc Trp Asn Ile Phe 1590	4779
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Asp	Ile	Ile	Gln	Lys	Tyr	Phe	Phe	Ser	Pro	Thr	Leu	Phe	Arg	Val	
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Ile	Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Arg	Gly	
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Ala	Lys	Gly	Ile	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser	Leu	
1640						1645					1650				
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1655						1660					1665				
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Ile	Tyr	Ser	Ile	Phe	Gly	Met	Ala	Asn	Phe	Ala	Tyr	Val	Lys	Trp	
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Glu	Ala	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Gln	Thr	Phe	Ala	Asn	
1685						1690					1695				
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Ser	Met	Leu	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp	Asp	
1700						1705					1710				
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Gly	Leu	Leu	Ser	Pro	Ile	Leu	Asn	Thr	Gly	Pro	Pro	Tyr	Cys	Asp	
1715						1720					1725				
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Phe	Leu	Ile	Val	Val	Asn	Met	Tyr	Ile	Ala	Ile	Ile	Leu	Glu	Asn	
1760						1765					1770				
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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	
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 cctttttcac	6095
Ile Val	
2015	
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<211> 2015

<212> PRT

<213> Homo sapiens

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 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

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 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

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			
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

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
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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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ccaagaagag gatgaggaga 20

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gaggcagtcg ctgacacc 18

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31

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 Trp Ala Arg Arg Glu Ser Ser Lys Gln Glu Ser Gln Pro Val Ser
 1 5 10 15

45

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