



(86) Date de dépôt PCT/PCT Filing Date: 2001/12/20
(87) Date publication PCT/PCT Publication Date: 2002/06/27
(45) Date de délivrance/Issue Date: 2013/01/29
(85) Entrée phase nationale/National Entry: 2003/06/19
(86) N° demande PCT/PCT Application No.: AU 2001/001648
(87) N° publication PCT/PCT Publication No.: 2002/050096
(30) Priorité/Priority: 2000/12/20 (AU PR 2203)

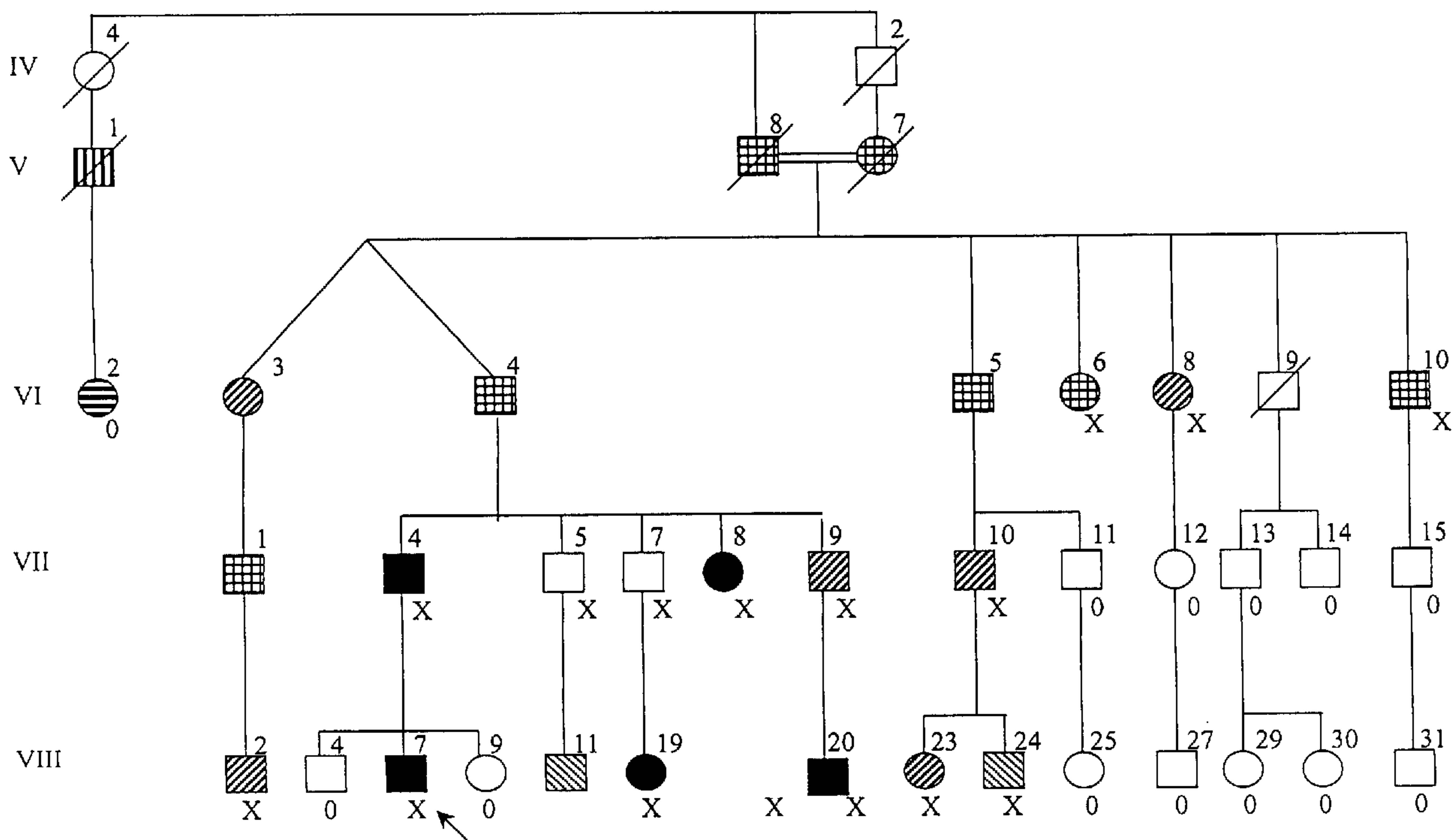
(51) Cl.Int./Int.Cl. *C12N 15/12* (2006.01),
A01K 67/027 (2006.01), *A61K 31/7105* (2006.01),
A61K 38/17 (2006.01), *A61K 39/395* (2006.01),
A61K 48/00 (2006.01), *A61P 25/08* (2006.01),
C07K 14/705 (2006.01), *C07K 16/28* (2006.01),
C12Q 1/68 (2006.01), *A61K 38/00* (2006.01)

(72) Inventeurs/Inventors:
WALLACE, ROBYN HEATHER, AU;
MULLEY, JOHN CHARLES, AU;
BERKOVIC, SAMUEL FRANK, AU

(73) Propriétaire/Owner:
BIONOMICS LIMITED, AU

(74) Agent: SMART & BIGGAR

(54) Titre : MUTATIONS DANS LA SOUS-UNITE ALPHA1 DU CANAL SODIQUE DU GENE NEURONAL, POLYPEPTIDES ASSOCIES, ET TRAITEMENT DU SYNDROME GEFS+ (EPILEPSIE GENERALISEE AVEC CRISES FEBRILES +)
(54) Title: MUTATIONS IN NEURONAL GENE SODIUM-CHANNEL ALPHA 1-SUBUNIT AND THEIR POLYPEPTIDES AND THEIR TREATMENT OF GENERALISED EPILEPSY WITH FEBRILE SEIZURES PLUS



(57) Abrégé/Abstract:

The mutations D188V, V1353L, I1656M in the neuronal gene sodium-channel alpha1-subunit, SCN1A, are disclosed. The methods of using their associated polypeptides for treating sodium channel dysfunction disorders including generalised epilepsy are also disclosed.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
27 June 2002 (27.06.2002)

PCT

(10) International Publication Number
WO 02/50096 A1(51) International Patent Classification⁷: **C07H 21/04**,
C07K 14/435, 16/18, C12N 15/12, 15/63, A61K 38/17,
39/395, 31/7105, 48/00, A61P 25/08**Frank** [AU/AU]; 7 Polo Parade, Caulfield North, VIC 3161
(AU).

(21) International Application Number: PCT/AU01/01648

(74) Agent: **GRIFFITH HACK**; GPO Box 3125, Brisbane,
QLD 4001 (AU).(22) International Filing Date:
20 December 2001 (20.12.2001)(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

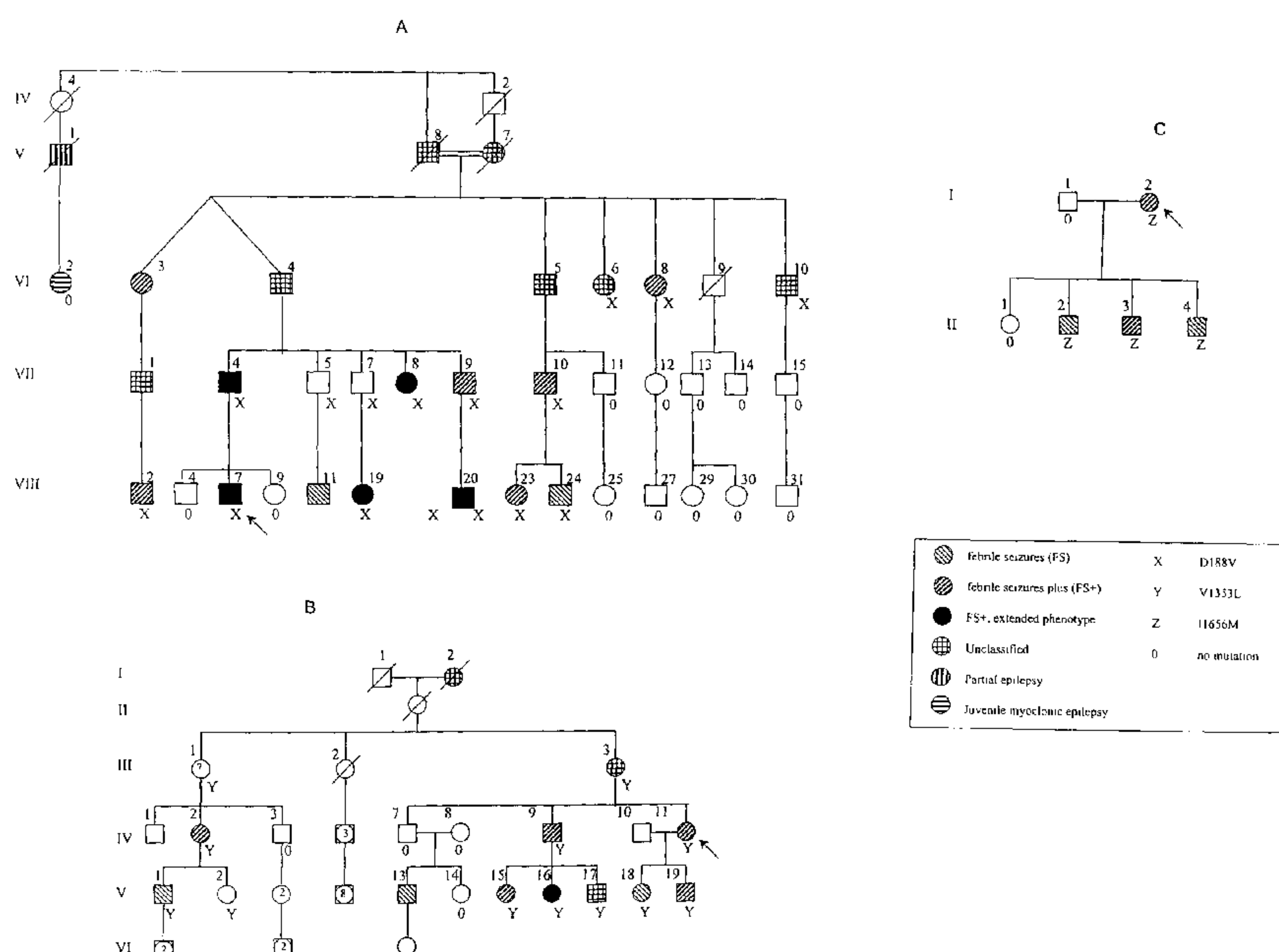
(30) Priority Data:
PR 2203 20 December 2000 (20.12.2000) AU(71) Applicant (*for all designated States except US*): **BIO-
NOMICS LIMITED** [AU/AU]; 31 Dalgleish Street,
Thebarton, S.A. 5031 (AU).(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **WALLACE, Robyn,
Heather** [AU/AU]; 51 Auricchio Avenue, St Marys S.A.
5042 (AU). **MULLEY, John, Charles** [AU/AU]; 13 Dunk-
ley Avenue, Firle, S.A. 5046 (AU). **BERKOVIC, Samuel**,**Published:**

— with international search report

[Continued on next page]

(54) Title: SODIUM-CHANNEL ALPHA1-SUBUNIT AND THEIR POLYPEPTIDES AND THEIR TREATMENT OF GENER-
ALISED EPILEPSY WITH FEBRILE SEIZURES PLUS(57) Abstract: The mutations D188V, V1353L, I1656M in the neuronal gene sodium-channel alpha1-subunit, SCN1A, are dis-
closed. The methods of using their associated polypeptides for treating sodium channel dysfunction disorders including generalised
epilepsy are also disclosed.

WO 02/50096 A1

WO 02/50096 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

- 1 -

Mutations in Neuronal gene sodium-channel alpha1-subunit and their polypeptides and their treatment
of generalised epilepsy with febrile seizures plus.

Technical Field

The present invention relates to mutations in the
5 alpha subunit of mammalian voltage-gated sodium channels
which are associated with idiopathic epilepsies and other
disorders such as malignant hyperthermia, myasthenia,
episodic ataxia, neuropathic and inflammatory pain,
Alzheimer's disease, Parkinson's disease, schizophrenia,
10 hyperekplexia, myotonias and cardiac arrhythmias, and to
polymorphisms in the gene encoding the alpha subunit.

Background Art

Generalised epilepsy with febrile seizures plus
15 (GEFS+; MIM 604236) was first described by Scheffer and
Berkovic (1997) and is now recognised as a common epilepsy
syndrome (Singh et al. 1999; Baulac et al. 1999; Moulard
et al. 1999; Peiffer et al. 1999; Scheffer et al. 2000).
Although GEFS+ is familial, it was initially difficult to
20 recognise it as a distinct syndrome, because of clinical
heterogeneity within each family. The common phenotypes
are typical febrile seizures (FS) and febrile seizures
plus (FS+); FS+ differs from FS in that the attacks with
fever continue beyond age 6 years and/or include afebrile
25 tonic-clonic seizures. Less common phenotypes include FS+
associated with absences, myoclonic or atonic seizures,
and even more-severe syndromes such as myoclonic-astatic
epilepsy. That such phenotypic diversity could be
associated with the segregation of a mutation in a single
30 gene was established with the identification of a mutation
in the voltage gated sodium channel beta-1 subunit gene
(SCN1B) (Wallace et al. 1998). This mutation (C121W)
changes a conserved cysteine residue, disrupting a
putative disulfide bridge, which results in in vitro loss
35 of function of the beta-1 subunit. Without a functional
beta-1 subunit the rate of inactivation of sodium channel
alpha subunits decreases, which may cause increased sodium

- 2 -

influx, resulting in a more depolarised membrane potential and hyperexcitability. Modifier genes or the environment may interact with the SCN1B gene to account for clinical heterogeneity, but the rarity of SCN1B mutations (Wallace et al. 1998) strongly suggested additional genes of large effect underlie GEFS+ in other families (Singh et al. 1999).

GEFS+ in four families has been mapped to chromosome 2q (Baulac et al. 1999; Moulard et al. 1999; Peiffer et al. 1999; Lopes-Cendes et al. 2000). Recently, mutations in the neuronal voltage gated sodium channel alpha-1 (SCN1A) subunit were described in two GEFS+ families (Escayg et al. 2000). The mutations (T875M and R1648H) are located in highly conserved S4 transmembrane segments of the channel which are known to have a role in channel gating. It was suggested that these mutations may reduce the rate of inactivation of SCN1A and therefore have a similar effect as the beta-1 subunit mutation.

GEFS+ is clearly a common complex disorder, with a strong genetic basis, incomplete penetrance and genetic and phenotypic heterogeneity. Febrile seizures occur in 3% of the population, and thus this phenotype may occur sporadically in GEFS+ families, in addition to occurring as a result of an inherited mutation in the GEFS+ gene (Wallace et al 1998). Also, although some families segregate an autosomal dominant gene of major effect, in many cases clinical genetic evidence, such as bilineality, suggests that for some small families the disorder is multifactorial (Singh et al 1999). Despite this, large families continue to be ascertained and with critical phenotypic analysis, they provide opportunities to localise and ultimately identify the genes involved.

Disclosure of the Invention

The present inventors have identified three new mutations in the alpha-1 subunit (SCN1A) of the voltage-gated sodium channel that are associated with epilepsy, in

- 3 -

particular generalized epilepsy with febrile seizures plus (GEFS+), and also determined the nucleotide sequence in that gene.

According to one aspect of the present invention
5 there is provided an isolated DNA molecule encoding a mutant alpha subunit of a mammalian voltage-gated sodium channel, wherein a mutation event selected from the group consisting of point mutations, deletions, insertions and rearrangements has occurred and said mutation event
10 disrupts the functioning of an assembled sodium channel so as to produce an epilepsy phenotype, with the proviso that the mutation event is not a C2624T transition or a G4943A transition in an alpha-1 subunit.

Preferably said mutation event is a point mutation.

15 Typically the mutation event occurs in an intracellular loop, preferably in the intracellular loop between transmembrane segments 2 and 3 of domain I, in the S4 segment of domain IV at amino acid position 1656, or in an S5 segment of a transmembrane domain. Preferably the
20 mutation creates a phenotype of generalised epilepsy with febrile seizures plus.

In one form of the invention the mutation is in exon 4 of SCN1A and results in replacement of a highly conserved aspartic acid residue with a valine residue at
25 amino acid position 188. The D188V mutation lies in the intracellular loop just outside the S3 segment of domain I of SCN1A and occurs as a result of an A to T nucleotide substitution at position 563 of the SCN1A coding sequence as shown in SEQ ID NO:1.

30 In a further form of the invention the mutation is in exon 21 of SCN1A and results in the replacement of a highly conserved valine residue with a leucine residue at amino acid position 1353. The V1353L mutation is located in the S5 segment of domain III of SCN1A and occurs as a
35 result of a G to C nucleotide substitution at position 4057 of the SCN1A coding sequence as shown in SEQ ID NO:3.

In a still further form of the invention the mutation

77748-6

-4-

is in exon 26 of SCN1A and results in the replacement of a highly conserved isoleucine residue with a methionine residue at amino acid position 1656. The I1656M mutation is located in the S4 segment of domain IV of SCN1A and occurs as a result of a C to G nucleotide substitution at position 4968 of the SCN1A coding
5 sequence as shown in SEQ ID NO: 5.

Hence, an embodiment of the invention relates to an isolated nucleic acid molecule encoding a mutant alpha-1 subunit of a mammalian voltage-gated sodium channel, wherein a point mutation has occurred and said mutation disrupts the functioning of an assembled sodium channel so as to produce an epilepsy
10 phenotype, said nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 5.

In another embodiment, the invention relates to an isolated nucleic acid molecule consisting of the nucleotide sequence set forth in SEQ ID NO: 5.

In another embodiment, the invention relates to an isolated polypeptide,
15 said polypeptide being a mutant alpha-1 subunit of a mammalian voltage-gated sodium channel, wherein a substitution has occurred and said substitution disrupts the functioning of an assembled sodium channel so as to produce an epilepsy phenotype, said polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 6.

20 In another embodiment, the invention relates to an isolated polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 6.

In another embodiment, the invention relates to an assembled mammalian voltage-gated sodium channel comprising a polypeptide as described above.

25 In another embodiment, the invention relates to a cell transformed with an isolated nucleic acid molecule as described above.

77748-6

-4a-

In another embodiment, the invention relates to an antibody that specifically binds a polypeptide as described above, but not a wild-type mammalian voltage-gated sodium channel.

5 In another embodiment, the invention relates to a monoclonal antibody that specifically binds the polypeptide as described herein, but not a wild-type mammalian voltage-gated sodium channel.

In another embodiment, the invention relates to an expression vector comprising a nucleic acid molecule as described above.

10 In another embodiment, the invention relates to the use of a nucleic acid molecule as described above in the diagnosis of generalised epilepsy with febrile seizures plus.

In another embodiment, the invention relates to the use of a polypeptide as described above in the diagnosis of generalised epilepsy with febrile seizures plus.

15 In another embodiment, the invention relates to the use of an antibody as described above in the diagnosis of generalised epilepsy with febrile seizures plus.

The nucleotide sequence of the gene set forth in SEQ ID NO: 89 also forms a part of the invention. In addition, the polymorphisms identified in Table 3 form part of the invention (SEQ ID Numbers: 7-9 and 11).

20 The present invention also encompasses DNA molecules in which one or more additional mutation events selected from the group consisting of point mutations, deletions, insertions and rearrangements have occurred. Any such DNA molecule will have the mutation associated with epilepsy described above and will be functional, but otherwise may vary significantly from the DNA molecules set forth in SEQ ID NO: 1, 3 and 5.

77748-6

-4b-

The nucleotide sequences of the present invention can be engineered using methods accepted in the art for a variety of purposes. These include, but are not limited to, modification of the cloning, processing, and/or expression of the gene product. PCR reassembly of gene fragments and the use of synthetic
5 oligonucleotides allow the engineering of the nucleotide sequences of the present invention. For example, oligonucleotide-mediated site-directed mutagenesis can introduce further mutations that create new restriction sites, alter expression patterns and produce splice variants etc.

Thus, a further embodiment of the invention relates to a method of
10 preparing a polypeptide as described above comprising the steps of: (1) culturing cells as described above under conditions effective for polypeptide production; and (2) harvesting the polypeptide.

As a result of the degeneracy of the genetic code, a number of polynucleotide sequences, some that may have minimal similarity to the
15 polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention includes each and every possible variation of a polynucleotide sequence that could be made by selecting combinations based on possible codon choices.

- 5 -

These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequences of the present invention, and all such variations are to be considered as being specifically disclosed.

The DNA molecules of this invention include cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified, or may contain non-natural or derivatised nucleotide bases as will be appreciated by those skilled in the art. Such modifications include labels, methylation, intercalators, alkylators and modified linkages. In some instances it may be advantageous to produce nucleotide sequences possessing a substantially different codon usage than that of the polynucleotide sequences of the present invention. For example, codons may be selected to increase the rate of expression of the peptide in a particular prokaryotic or eukaryotic host corresponding with the frequency that particular codons are utilized by the host. Other reasons to alter the nucleotide sequence without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring mutated sequence.

The invention also encompasses production of DNA sequences of the present invention entirely by synthetic chemistry. Synthetic sequences may be inserted into expression vectors and cell systems that contain the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements may include regulatory sequences, promoters, 5' and 3' untranslated regions and specific initiation signals (such as an ATG initiation codon and Kozak consensus sequence) which allow more efficient translation of sequences encoding the polypeptides of the present invention. In cases where the complete coding

- 6 -

sequence, including the initiation codon and upstream regulatory sequences, are inserted into the appropriate expression vector, additional control signals may not be needed. However, in cases where only coding sequence, or a
5 fragment thereof, is inserted, exogenous translational control signals as described above should be provided by the vector. Such signals may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the
10 particular host cell system used (Scharf et al., 1994).

The invention also includes nucleic acid molecules that are the complements of the sequences described herein.

According to still another aspect of the present
15 invention there is provided an isolated DNA molecule consisting of the nucleotide sequence set forth in any one of SEQ ID NOS:1, 3, 5, 7, 8, 9, 11 and 89.

The present invention allows for the preparation of purified polypeptides or proteins from the polynucleotides
20 of the present invention, or variants thereof. In order to do this, host cells may be transformed with a DNA molecule as described above. Typically said host cells are transfected with an expression vector comprising a DNA molecule according to the invention. A variety of
25 expression vector/host systems may be utilized to contain and express sequences encoding polypeptides of the invention. These include, but are not limited to, microorganisms such as bacteria transformed with plasmid or cosmid DNA expression vectors; yeast transformed with
30 yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); or mouse or other animal or human tissue cell systems. Mammalian cells can be used to express a protein using various expression vectors including plasmid, cosmid and
35 viral systems such as a vaccinia virus expression system. The invention is not limited by the host cell employed.

The polynucleotide sequences, or variants thereof, of

- 7 -

the present invention can be stably expressed in cell lines to allow long term production of recombinant proteins in mammalian systems. Sequences encoding the polypeptides of the present invention can be transformed
5 into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. The selectable marker confers resistance to a selective agent, and its presence allows growth and
10 recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

The protein produced by a transformed cell may be
15 secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode a protein may be designed to contain signal sequences which direct secretion of the
20 protein through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include,
25 but are not limited to, acetylation, glycosylation, phosphorylation, and acylation. Post-translational cleavage of a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells having specific cellular
30 machinery and characteristic mechanisms for post-translational activities (e.g., CHO or HeLa cells), are available from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the foreign protein.

35 When large quantities of the gene are needed, such as for antibody production, vectors which direct high levels of expression of this protein may be used, such as those

- 8 -

containing the T5 or T7 inducible bacteriophage promoter. The present invention also includes the use of the expression systems described above in generating and isolating fusion proteins which contain important functional domains of the protein. These fusion proteins are used for binding, structural and functional studies as well as for the generation of appropriate antibodies.

In order to express and purify the protein as a fusion protein, the appropriate polynucleotide sequences of the present invention are inserted into a vector which contains a nucleotide sequence encoding another peptide (for example, glutathione-s-transferase). The fusion protein is expressed and recovered from prokaryotic or eukaryotic cells. The fusion protein can then be purified by affinity chromatography based upon the fusion vector sequence. The desired protein is then obtained by enzymatic cleavage of the fusion protein.

Fragments of polypeptides of the present invention may also be produced by direct peptide synthesis using solid-phase techniques. Automated synthesis may be achieved by using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments of this protein may be synthesized separately and then combined to produce the full length molecule.

According to still another aspect of the present invention there is provided an isolated polypeptide, said polypeptide being a mutant alpha subunit of a mammalian voltage-gated sodium channel, wherein a mutation event selected from the group consisting of point mutations, deletions, insertions and rearrangements has occurred and said mutation event disrupts the functioning of an assembled sodium channel so as to produce an epilepsy phenotype, with the proviso that said mutation event is not a T875M transition or a R1648H transition in an alpha-1 subunit.

Preferably said mutation event occurs in an intracellular loop, preferably in the intracellular loop

- 9 -

between transmembrane segments 2 and 3 in domain I, in the S4 segment of domain IV at amino acid position 1656, or in an S5 segment of a transmembrane domain of SCN1A. Preferably the mutation creates a phenotype of generalised epilepsy with febrile seizures plus.

In one form of the invention the mutation event is a substitution in which a highly conserved aspartic acid residue is replaced with a valine residue located in the intracellular domain located just outside the S3 segment of domain I of SCN1A. Preferably the substitution is a D188V transition as illustrated in SEQ ID NO:2.

In a further form of the invention the mutation event is a substitution in which a highly conserved valine residue is replaced with a leucine residue located in the S5 segment of domain III of SCN1A. Preferably the substitution is a V1353L transition as illustrated in SEQ ID NO:4.

In a still further form of the invention the mutation event is a substitution in which a highly conserved isoleucine residue is replaced with a methionine residue located in the S4 segment of domain IV of SCN1A. Preferably the substitution is a I1656M transition as illustrated in SEQ ID NO:6.

In addition, the polymorphisms identified in Table 3 form part of the invention (SEQ ID Numbers:10 and 12). These polymorphisms may reflect changes in SCN1A which result in subtle changes of function of the sodium channel. These subtle changes may predispose individuals to epilepsy and when expressed in combination with other ion channel changes may lead to specific sub-types of the disease (see PCT/AU01/00872).

The isolated polypeptides of the present invention may have been subjected to one or more mutation events selected from the group consisting of substitutions, deletions, insertions and rearrangements in addition to the mutation associated with epilepsy. Typically these mutation events are conservative substitutions.

- 10 -

According to still another aspect of the present invention there is provided an isolated polypeptide comprising the sequence set forth in any one of SEQ ID NO:2, 4, 6, 10 and 12.

5 According to still another aspect of the present invention there is provided a polypeptide consisting of the amino acid sequence set forth in any one of SEQ ID NO:2, 4, 6, 10 and 12.

10 According to still another aspect of the present invention there is provided an isolated polypeptide complex, said polypeptide complex being an assembled mammalian voltage-gated sodium channel, wherein a mutation event selected from the group consisting of substitutions, deletions, insertions and rearrangements has occurred in
15 the alpha subunit of the complex. Mutations include those in the intracellular loop between transmembrane segments 2 and 3, the S4 segment of domain IV at amino acid position 1656, or in an S5 segment of a transmembrane domain of the alpha subunit. In a particular aspect an assembled
20 mammalian voltage-gated sodium channel bearing any such mutation in the alpha subunit will produce a phenotype of epilepsy, in particular generalised epilepsy with febrile seizures plus, or other disorders associated with sodium channel dysfunction including, but not restricted to,
25 malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita and potassium aggravated
30 myotonia as well as cardiac arrhythmias such as long QT syndrome.

In a particular aspect there is provided a complex, being an assembled mammalian voltage-gated sodium channel, bearing a mutation in the intracellular loop between
35 transmembrane segments 2 and 3, the S4 segment of domain IV at amino acid position 1656, or in an S5 segment of a transmembrane domain of the SCN1A subunit of the channel.

- 11 -

According to still another aspect of the present invention there is provided a method of preparing a polypeptide, said polypeptide being a mutant alpha subunit of a mammalian voltage-gated sodium channel, comprising
5 the steps of:

- (1) culturing host cells transfected with an expression vector comprising a nucleic acid molecule as described above under conditions effective for polypeptide production; and
- 10 (2) harvesting the mutant alpha subunit.

The mutant alpha subunit may also be allowed to assemble with other subunits of the sodium channel, whereby the assembled mutant sodium channel is harvested.

According to still another aspect of the invention
15 there is provided a polypeptide which is the product of the process described above.

Substantially purified protein or fragments thereof can then be used in further biochemical analyses to establish secondary and tertiary structure for example by
20 X-ray crystallography of crystals of the proteins or by nuclear magnetic resonance (NMR). Determination of structure allows for the rational design of pharmaceuticals to interact with the mutated sodium channel, alter the overall sodium channel protein charge
25 configuration or charge interaction with other proteins, or to alter its function in the cell.

It will be appreciated that, having identified mutations involved in epilepsy in these proteins, the mutant sodium channel alpha subunits will be useful in
30 further applications which include a variety of hybridisation and immunological assays to screen for and detect the presence of either a normal or mutated gene or gene product. The invention also enables therapeutic methods for the treatment of epilepsy and enables methods
35 for the diagnosis of epilepsy with both wild-type and mutant nucleic acid molecules. In particular the invention enables treatment and diagnosis of generalised epilepsy

- 12 -

with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction, as mentioned above.

5 Therapeutic Applications

According to one aspect of the invention there is provided a method of treating epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel
10 dysfunction, including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia
15 congenita and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome, comprising administering a selective antagonist, agonist or modulator of the sodium channel when a mutation event as described above has occurred, in particular, when it contains a
20 mutation in the intracellular loop between transmembrane segments 2 and 3, in the S4 segment of domain IV at amino acid position 1656, or in an S5 segment of a transmembrane domain of an alpha subunit.

In still another aspect of the invention there is
25 provided the use of a selective antagonist, agonist or modulator of the sodium channel when a mutation event as described above has occurred, in particular, to a sodium channel when it contains a mutation in the intracellular loop between transmembrane segments 2 and 3, in the S4
30 segment of domain IV at amino acid position 1656, or in an S5 segment of a transmembrane domain of an alpha subunit, said mutation being causative of a disorder including epilepsy, in particular generalised epilepsy with febrile seizures plus as well as other disorders associated with
35 sodium channel dysfunction, including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease,

- 13 -

Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome, in the manufacture of a medicament for the treatment of the disorder.

In one aspect of the invention a suitable antagonist or modulator will restore wild-type function to the sodium channels that contain a mutation in an alpha subunit including those that form part of this invention.

Using methods well known in the art, a mutant sodium channel may be used to produce antibodies specific for the mutant channel that is causative of the disease or to screen libraries of pharmaceutical agents to identify those that specifically bind the mutant sodium channel.

In one aspect, an antibody, which specifically binds to a mutant sodium channel, may be used directly as an antagonist or modulator, or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues that express the mutant sodium channel.

In a still further aspect of the invention there is provided an antibody which is immunologically reactive with a polypeptide as described above, but not with a wild-type sodium channel or subunit thereof.

In particular, there is provided an antibody to an assembled sodium channel containing a mutation causative of a disorder as described above, in a subunit comprising the receptor. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies as would be understood by the person skilled in the art.

For the production of antibodies, various hosts including rabbits, rats, goats, mice, humans, and others may be immunized by injection with a polypeptide as described or with any fragment or oligopeptide thereof which has immunogenic properties. Various adjuvants may be used to increase immunological response and include, but

- 14 -

are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface-active substances such as lysolecithin. Adjuvants used in humans include BCG (bacilli Calmette-Guerin) and Corynebacterium parvum.

5 It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to the mutant sodium channel have an amino acid sequence consisting of at least 5 amino acids, and, more preferably, of at least 10 amino acids. It is also preferable that these oligopeptides,
10 peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of sodium channel amino acids may be fused with those of another protein, such as KLH,
15 and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to a mutant sodium channel may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the
20 hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (For example, see Kohler et al., 1975; Kozbor et al., 1985; Cote et al., 1983; Cole et al., 1984).

Antibodies may also be produced by inducing in vivo
25 production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (For example, see Orlandi et al., 1989; Winter et al., 1991).

Antibody fragments which contain specific binding
30 sites for a mutant sodium channel may also be generated. For example, such fragments include, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression
35 libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (For example, see Huse et al., 1989).

- 15 -

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between a sodium channel and its specific antibody. A two-site, monoclonal-based immunoassay utilizing antibodies reactive to two non-interfering sodium channel epitopes is preferred, but a competitive binding assay may also be employed.

In a further aspect of the invention there is provided a method of treating epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction, including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome, comprising administering an isolated DNA molecule which is the complement (antisense) of any one of the DNA molecules described above and which encodes an RNA molecule that hybridizes with the mRNA encoding a mutant sodium channel alpha subunit, to a subject in need of such treatment.

Typically, a vector expressing the complement of the polynucleotides of the invention may be administered to a subject in need of such treatment. Antisense strategies may use a variety of approaches including the use of antisense oligonucleotides, injection of antisense RNA, ribozymes, DNazymes and transfection of antisense RNA expression vectors. Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken

- 16 -

from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (For example, see Goldman et al., 1997).

In a still further aspect of the invention there is provided the use of an isolated DNA molecule which is the complement of a DNA molecule of the invention and which encodes an RNA molecule that hybridizes with the mRNA encoding a mutant sodium channel alpha subunit, in the manufacture of a medicament for the treatment of epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction, including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome.

In a further aspect, a suitable agonist or modulator may include a small molecule that can restore wild-type activity of the sodium channel containing mutations in the alpha subunit as described above, or may include an antibody to a mutant sodium channel that is able to restore channel function to a normal level.

Small molecules suitable for therapeutic applications may be identified using nucleic acids and peptides of the invention in drug screening applications as described below.

In further embodiments, any of the agonists, antagonists, modulators, antibodies, complementary sequences or vectors of the invention may be administered alone or in combination with other appropriate therapeutic agents. Selection of the appropriate agents may be made by

- 17 -

those skilled in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using
5 this approach, therapeutic efficacy with lower dosages of each agent may be possible, thus reducing the potential for adverse side effects.

Drug screening

According to still another aspect of the invention,
10 peptides of the invention, particularly purified mutant sodium channel alpha subunit polypeptide and cells expressing these, are useful for the screening of candidate pharmaceutical agents in a variety of techniques. It will be appreciated that therapeutic agents
15 useful in the treatment of epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction, including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and
20 inflammatory pain, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome, are likely
25 to show binding affinity to the polypeptides of the invention.

Such techniques include, but are not limited to, utilising eukaryotic or prokaryotic host cells that are stably transformed with recombinant molecules expressing
30 the polypeptide or fragment, preferably in competitive binding assays. Binding assays will measure the formation of complexes between a mutated sodium channel alpha subunit polypeptide or fragment and the agent being tested, or will measure the degree to which an agent being
35 tested will interfere with the formation of a complex between a mutated sodium channel alpha subunit polypeptide or fragment and a known ligand.

- 18 -

Another technique for drug screening provides high-throughput screening for compounds having suitable binding affinity to the mutant sodium channel alpha subunit polypeptides or sodium channels containing these (see PCT published application WO84/03564). In this stated technique, large numbers of small peptide test compounds can be synthesised on a solid substrate and can be assayed through mutant sodium channel or mutant sodium channel alpha subunit polypeptide binding and washing. Bound mutant sodium channel or mutant sodium channel alpha subunit polypeptide is then detected by methods well known in the art. In a variation of this technique, purified polypeptides of the invention can be coated directly onto plates to identify interacting test compounds.

The invention also contemplates the use of competition drug screening assays in which neutralizing antibodies capable of specifically binding the mutant sodium channel compete with a test compound for binding thereto. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants of the mutant sodium channel.

The invention is particularly useful for screening compounds by using the polypeptides of the invention in transformed cells, transfected or injected oocytes, or animal models bearing mutated sodium channel alpha subunits (particularly those of the invention) such as transgenic animals or gene targeted (knock-in) animals (see below). A particular drug is added to the cells in culture or administered to an animal model containing a mutant sodium channel alpha subunit and the effect on the current of the channel is compared to the current of a cell or animal containing the wild-type sodium channel. Drug candidates that alter the current to a more normal level are useful for treating or preventing epilepsy, in particular generalised epilepsy with febrile seizures plus as well as other disorders associated with sodium channel dysfunction, as described above.

- 19 -

The polypeptides of the present invention may also be used for screening compounds developed as a result of combinatorial library technology. This provides a way to test a large number of different substances for their ability to modulate activity of a polypeptide. The use of peptide libraries is preferred (see WO 97/02048) with such libraries and their use known in the art.

A substance identified as a modulator of polypeptide function may be peptide or non-peptide in nature. Non-peptide "small molecules" are often preferred for many *in vivo* pharmaceutical applications. In addition, a mimic or mimetic of the substance may be designed for pharmaceutical use. The design of mimetics based on a known pharmaceutically active compound ("lead" compound) is a common approach to the development of novel pharmaceuticals. This is often desirable where the original active compound is difficult or expensive to synthesise or where it provides an unsuitable method of administration. In the design of a mimetic, particular parts of the original active compound that are important in determining the target property are identified. These parts or residues constituting the active region of the compound are known as its pharmacophore. Once found, the pharmacophore structure is modelled according to its physical properties using data from a range of sources including x-ray diffraction data and NMR. A template molecule is then selected onto which chemical groups which mimic the pharmacophore can be added. The selection can be made such that the mimetic is easy to synthesise, is likely to be pharmacologically acceptable, does not degrade *in vivo* and retains the biological activity of the lead compound. Further optimisation or modification can be carried out to select one or more final mimetics useful for *in vivo* or clinical testing.

It is also possible to isolate a target-specific antibody and then solve its crystal structure. In principle, this approach yields a pharmacophore upon which

- 20 -

subsequent drug design can be based as described above. It may be possible to avoid protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody.

5 As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analogue of the original receptor. The anti-id could then be used to isolate peptides from chemically or biologically produced peptide banks.

10 Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

15 Diagnostic applications

Polynucleotide sequences of the invention may be used for the diagnosis of epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction,

20 including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita

25 and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome, and the use of the DNA molecules of the invention in diagnosis of these disorders, is therefore contemplated.

In another embodiment of the invention, the

30 polynucleotides that may be used for diagnostic purposes include oligonucleotide sequences, genomic DNA and complementary RNA and DNA molecules. The polynucleotides may be used to detect and quantitate gene expression in biological samples. Genomic DNA used for the diagnosis

35 may be obtained from body cells, such as those present in the blood, tissue biopsy, surgical specimen, or autopsy material. The DNA may be isolated and used directly for

- 21 -

detection of a specific sequence or may be amplified by the polymerase chain reaction (PCR) prior to analysis. Similarly, RNA or cDNA may also be used, with or without PCR amplification. To detect a specific nucleic acid sequence, hybridisation using specific oligonucleotides, restriction enzyme digest and mapping, PCR mapping, RNase protection, and various other methods may be employed. For instance direct nucleotide sequencing of amplification products from the sodium channel subunits can be employed. Sequence of the sample amplicon is compared to that of the wild-type amplicon to determine the presence (or absence) of nucleotide differences.

According to a further aspect of the invention there is provided the use of a polypeptide as described above in the diagnosis of epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction, as described above.

When a diagnostic assay is to be based upon mutant proteins constituting a sodium channel, a variety of approaches are possible. For example, diagnosis can be achieved by monitoring differences in the electrophoretic mobility of normal and mutant alpha subunit proteins that form part of the sodium channel. Such an approach will be particularly useful in identifying mutants in which charge substitutions are present, or in which insertions, deletions or substitutions have resulted in a significant change in the electrophoretic migration of the resultant protein. Alternatively, diagnosis may be based upon differences in the proteolytic cleavage patterns of normal and mutant proteins, differences in molar ratios of the various amino acid residues, or by functional assays demonstrating altered function of the gene products.

In another aspect, antibodies that specifically bind mutant sodium channels may be used for the diagnosis of epilepsy, or in assays to monitor patients being treated with agonists, antagonists, modulators or inhibitors of

- 22 -

the mutant sodium channel. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays to detect mutant sodium channels include methods that utilize the antibody and a label to detect a mutant sodium channel in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labelled by covalent or non-covalent attachment of a reporter molecule.

10 A variety of protocols for measuring the presence of mutant sodium channels, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing epilepsy, in particular generalised epilepsy with febrile seizures plus, as well as other disorders associated with sodium channel dysfunction, as described above. The expression of a mutant channel is established by combining body fluids or cell extracts taken from test mammalian subjects, preferably human, with antibody to the channel under conditions suitable for complex formation. The amount of complex formation may be quantitated by various methods, preferably by photometric means. Antibodies specific for the mutant channel will only bind to individuals expressing the said mutant channel and not to individuals expressing only wild-type channels (ie normal individuals). This establishes the basis for diagnosing the disease.

Once an individual has been diagnosed with the disorder, effective treatments can be initiated. These may include administering a selective modulator of the mutant channel or an antagonist to the mutant channel such as an antibody or mutant complement as described above. Alternative treatments include the administering of a selective agonist or modulator to the mutant channel so as to restore channel function to a normal level.

35

Microarray

In further embodiments, complete cDNAs,

- 23 -

oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as probes in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents. Microarrays may be prepared, used, and analyzed using methods known in the art. (For example, see Schena et al., 1996; Heller et al., 1997).

According to a further aspect of the present invention, neurological material obtained from animal models generated as a result of the identification of specific sodium channel alpha subunit human mutations, particularly those disclosed in the present invention, can be used in microarray experiments. These experiments can be conducted to identify the level of expression of specific sodium channel alpha subunits, or any cDNA clones from whole-brain libraries, in epileptic brain tissue as opposed to normal control brain tissue. Variations in the expression level of genes, including sodium channel alpha subunits, between the two tissues indicates their involvement in the epileptic process either as a cause or consequence of the original sodium channel mutation present in the animal model. Microarrays may be prepared, as described above.

30 Transformed hosts

The present invention also provides for the production of genetically modified (knock-out, knock-in and transgenic), non-human animal models transformed with the DNA molecules of the invention. These animals are useful for the study of the function of a sodium channel, to study the mechanisms of disease as related to a sodium channel, for the screening of candidate pharmaceutical

- 24 -

compounds, for the creation of explanted mammalian cell cultures which express a mutant sodium channel and for the evaluation of potential therapeutic interventions.

Animal species which are suitable for use in the animal models of the present invention include, but are not limited to, rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs, and non-human primates such as monkeys and chimpanzees. For initial studies, genetically modified mice and rats are highly desirable due to their relative ease of maintenance and shorter life spans. For certain studies, transgenic yeast or invertebrates may be suitable and preferred because they allow for rapid screening and provide for much easier handling. For longer term studies, non-human primates may be desired due to their similarity with humans.

To create an animal model for a mutated sodium channel several methods can be employed. These include but are not limited to generation of a specific mutation in a homologous animal gene, insertion of a wild type human gene and/or a humanized animal gene by homologous recombination, insertion of a mutant (single or multiple) human gene as genomic or minigene cDNA constructs using wild type or mutant or artificial promoter elements or insertion of artificially modified fragments of the endogenous gene by homologous recombination. The modifications include insertion of mutant stop codons, the deletion of DNA sequences, or the inclusion of recombination elements (lox p sites) recognized by enzymes such as Cre recombinase.

To create a transgenic or gene targeted (knock-in) mouse, which are preferred, a mutant version of a sodium channel alpha subunit can be inserted into a mouse germ line using standard techniques of oocyte microinjection, or transfected into embryonic stem cells, respectively. Alternatively, if it is desired to inactivate or replace an endogenous sodium channel alpha subunit gene, homologous recombination using embryonic stem cells may be

- 25 -

applied.

For oocyte injection, one or more copies of the mutant sodium channel alpha subunit gene can be inserted into the pronucleus of a just-fertilized mouse oocyte. This oocyte is then reimplanted into a pseudo-pregnant foster mother. The liveborn mice can then be screened for integrants using analysis of tail DNA or DNA from other tissues for the presence of the particular human subunit gene sequence. The transgene can be either a complete genomic sequence injected as a YAC, BAC, PAC or other chromosome DNA fragment, a complete cDNA with either the natural promoter or a heterologous promoter, or a minigene containing all of the coding region and other elements found to be necessary for optimum expression.

According to still another aspect of the invention there is provided the use of genetically modified non-human animals as described above for the screening of candidate pharmaceutical compounds.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

Throughout this specification and the claims, the words "comprise", "comprises" and "comprising" are used in a non-exclusive sense, except where the context requires otherwise.

Brief Description of the Drawings

Preferred forms of the invention are described, by way of example only, with reference to the following examples and the accompanying drawings, in which:

Figure 1. Generalised epilepsy with febrile seizures plus (GEFS+) pedigrees are shown for the three families. DNA was not available from those individuals not assigned a letter (X, Y, or Z) or a 0. A: Pedigree of an Australian family with individual numbering for this

- 26 -

family based on Figure 1 in Scheffer & Berkovic (1997).
B: Pedigree of an Ashkenazi family. C: Pedigree of a
Druze family.

5 Figure 2. Schematic of the alpha subunit of the
sodium channel (SCN1A), showing the position of the three
mutations identified in this study.

Figure 3. Sodium channel amino acid alignments.
Alignment of sodium channel amino acids surrounding the
three SCN1A mutations.

10

Modes for Performing the Invention

Example 1: Clinical diagnosis of affected family members

15 A group of 53 unrelated probands with GEFS+
phenotypes were studied. These subjects were ascertained
on the basis of twin and family studies and on the basis
of routine clinical practice. Phenotypes in probands and
family members were classified as described elsewhere
(Scheffer & Berkovic 1997; Singh et al 1999). Familial
cases (n=36) were those in which at least one first-degree
20 relative of the proband had a phenotype within the GEFS+
spectrum. Informed consent was obtained from all subjects.

The Australian family in Figure 1A, which has been
described extensively elsewhere (Scheffer & Berkovic,
1997; Lopes-Cendes et al, 2000), is the original pedigree
25 leading to the initial delineation and description of the
GEFS+ syndrome.

The Israeli family in Figure 1B is of Ashkenazi
origin and spans six generations. Twelve family members
had seizures. In the two oldest members (I-2, III-3)
30 seizures had occurred in childhood but the data were
insufficient to allow classification of the phenotype. Of
the 10 other family members who had seizures, 3 had
febrile seizures with onset at age 9-13 months. All
attacks occurred with fever and offset occurred between 1
and 4 years with 1 to 7 attacks each. Five had febrile
35 seizures plus with onset at age 9-24 months, offset
between 5 and 41 years and 2 to 15 attacks each. Seizures

- 27 -

during childhood were a mixture of febrile seizures and afebrile tonic-clonic seizures, whereas the rarely occurring seizures during teenage and adult years were all afebrile. Subject V-16 had a more severe phenotype with approximately 20 febrile seizures at age 6 months to 5 years, 10 afebrile tonic-clonic seizures at age 5 to 15 years and occasional complex partial seizures associated with mild learning difficulties. She was classified as having febrile seizures plus and complex partial seizures. Her older sister (V-15) had typical febrile seizures plus, but their younger brother (V-17), aged 14 years, had no febrile seizures but had two afebrile tonic-clonic seizures at ages 12 years 6 months and 14 years. For purposes of linkage analysis, he was regarded as affected, although he had only afebrile tonic-clonic seizures. All affected subjects were of normal or superior intellect, except V-16 (see above) and all had a normal neurological examination. Electroencephalography (EEG) studies had been performed infrequently during the active phase of the epilepsy, and the results usually either were normal or were reported to show generalised discharges.

The second Israeli family was of Druze origin; the parents were from different but proximate villages and were not known to be related. This family spans two generations, and four family members had seizures (Figure 1C). The proband aged 41 years (I-2) had had hundreds of tonic-clonic seizures, sometimes with fever. These began at age 4 years and continued, at a rate of approximately one per month, until the time of the study. The proband was mildly intellectually impaired. EEG showed generalized irregular spike-wave and polyspike-wave discharges, and febrile seizures plus was diagnosed. Of her four children, the oldest was unaffected (II-1), two had febrile seizures (II-2, II-4) and one had febrile seizures plus (II-3).

Example 2: Isolation and sequencing of SCN1A genomic clones

- 28 -

At the commencement of this study the full-length sequence of the human SCN1A gene was not known. To determine this sequence a human BAC library obtained from Genome Systems was initially screened to identify human genomic sequence clones containing the SCN1A gene. The BAC filters were screened with a PCR product amplified with the primer pair 5' AGATGACCAGAGTGAATATGTGACTAC 3' (SEQ ID NO:13) and 5' CCAATGGTAAAATAATAATGGCGT 3' (SEQ ID NO:14) designed from the partial cDNA sequence of human SCN1A (Genbank Accession Number X65362).

The BAC filters were hybridised and washed according to manufacturers recommendations. Initially, membranes were individually pre-hybridised in large glass bottles for at least 2 hours in 20 ml of 6X SSC; 0.5% SDS; 5X Denhardt's; 100 ug/ml denatured salmon sperm DNA at 65°C. Overnight hybridisations with [α -³²P]dCTP labelled probes were performed at 65°C in 20 ml of a solution containing 6X SSC; 0.5% SDS; 100 ug/ml denatured salmon sperm DNA. Filters were washed sequentially in solutions of 2X SSC; 0.5% SDS (room temperature 5 minutes), 2X SSC; 0.1% SDS (room temperature 15 minutes) and 0.1X SSC; 0.5% SDS (37°C 1 hour if needed).

A number of BAC clones were identified from this hybridisation and BAC129e04 was selected for subcloning and sequencing. DNA from this BAC clone was sheared by nebulisation (10psi for 45 seconds). Sheared DNA was then blunt ended using standard methodologies (Sambrook et al., 1989) and run on an agarose gel in order to isolate DNA in the 2-4 Kb size range. These fragments were cleaned from the agarose using QIAquick columns (Qiagen), ligated into puc18 and used to transform competent XL-1 Blue *E. coli* cells. DNA was isolated from transformed clones and was sequenced using vector specific primers on an ABI377 sequencer to generate 1X coverage of the BAC clone. Sequence data were assembled in contigs using the Phred, Phrap and Gap4 high throughput sequencing software. Exon-intron boundaries were predicted based on the rat *Scn1a*

- 29 -

cDNA sequence (Genbank Accession Number M22253) due to the full length human cDNA sequence of SCN1A not being known.

The human SCN1A gene was determined to be 8,381 base pair in length and is organised into 27 exons spanning
5 over 100 Kb of genomic DNA. To facilitate a comparison with related sodium channels SCN4A, SCN5A and SCN8A, the first untranslated exon of SCN1A is designated exon 1A and the second exon, containing the start codon, remains exon 1 (Table 1). The SCN1A gene shows high homology to SCN2A
10 and SCN3A at both the DNA and protein level. The close proximity of these genes to each other on chromosome 2 indicates likely duplication events during the evolution of the sodium channel gene family. Compared to SCN4A and SCN8A, additional sequence is present in the 3'UTR of
15 SCN1A, giving the final exon an overall length of ~3.3 Kb.

Inspection of the splice junctions of SCN1A shows that there is close agreement with consensus splice motifs, with all introns bounded by GT-AG, except for two
20 (introns 2 and 23). These introns exhibit deviation from the consensus splice pattern and are bounded by AT-AC terminal dinucleotides. These rare splice site variations are conserved in other characterised sodium channel subunits (SCN4A, SCN8A and the more distantly related SCN5A), indicating their ancient origin.

25 The intron positions are also highly conserved between sodium channel subunits, with most variation seen in the region that codes for the cytoplasmic loop between domains I and II of the gene (Table 1). Within this region, alternative splicing of exon 11 of SCN1A was found
30 that was comparable to the alternative splicing of exon 10B in SCN8A (Plummer et al. 1998). Cytoplasmic loop 1 varies in both length and composition and is the proposed site of functional diversity among different sodium channels (Plummer & Meisler, 1999).

35

Example 3: Analysis of SCN1A for mutations in epilepsy

The determination of the genomic structure of SCN1A

- 30 -

allowed the design of intronic primers (Table 2 and SEQ ID Numbers:15-88) to amplify each of the 27 exons of SCN1A in order to test for mutations in patients with generalised epilepsy with febrile seizures plus (GEFS+). A total of 53
5 unrelated patients (as described above) were screened by fluorescent single stranded conformation polymorphism (SSCP) analysis.

HEX-labelled primers were designed to amplify all exons of SCN1A (Table 2). A 30 ng sample of patient DNA
10 was amplified in a total volume of 10 ul. Products were separated on non-denaturing 4% polyacrylamide gels containing 2% glycerol using the GelScan 2000 (Corbett Research). PCR products showing a conformational change were reamplified from 100 ng of genomic DNA with
15 unlabelled primers and sequenced using the BigDye Terminator ready reaction kit (Perkin Elmer) according to manufacturers instructions.

A total of 53 unrelated patients with GEFS+ were screened by fluorescent SSCP, including two families
20 consistent with mapping to the same location as SCN1A on chromosome 2 (Figures 1A and 1B). No mutations were found in 17 sporadic cases of GEFS+ that were tested. Of the 36 families tested, 3 were found to have point mutations in SCN1A, which alter the amino acid sequence and are not
25 present in the control population (n=60). The phenotype in the family in Figure 1A previously had been mapped to chromosome 2 (Lopes-Cendes et al. 2000) and carries an A to T mutation at position 563 of the SCN1A coding sequence. This mutation segregates with affected family
30 members. This mutation in exon 4 of SCN1A results in a D188V amino acid substitution that lies just outside the S3 segment of domain I (Figure 2). The aspartic acid residue is conserved in all identified sodium channels in humans as well as in many different animal species, except
35 the jellyfish which has an arginine at this residue and the flatworm which has a serine (Figure 3). The published rat Scn2a sequence (Genbank Accession Number NM_012647)

- 31 -

also has an arginine in place of the aspartic acid at residue 188.

A mutation in exon 21 (G to C nucleotide change at position 4057 of the SCN1A coding sequence) was found to segregate with GEFS+ in the Ashkenazi family (Figure 1B). This mutation changes a highly conserved amino acid (V1353L) located in the S5 segment of domain III (Figure 2). One family member (V-13) did not carry the mutation (Figure 1B). This was determined by testing the DNA of a parent of this family member, since the subjects DNA was unavailable. This individual, who had typical febrile seizures that terminated at an early age, is likely to be a phenocopy. Mutations in the S5 segment of SCN4A that cause hyperkalemic periodic paralysis have been shown also to affect the rate of channel inactivation (Bendahhou et al., 1999)

A third mutation (C to G nucleotide change at position 4968 of the SCN1A coding sequence) discovered in the Druze family (Figure 1C), changes an amino acid (I1656M) in the S4 segment of domain IV (Figure 2). The S4 segment has a role in channel gating and mutations in this region of SCN1A reduce the rate of inactivation (Kuhn and Greef, 1996).

During the mutation screen of SCN1A several single nucleotide polymorphisms (SNPs) were identified (Table 3). The R1928G variant was found at low frequency in both GEFS+ and control populations. The T1067A variant was common in both populations and the remaining SNPs identified did not alter the amino acid sequence of SCN1A (Table 3).

Example 4: Analysis of a mutated sodium channels and sodium channel alpha subunits

The following methods are used to determine the structure and function of mutated sodium channel or sodium channel alpha subunits.

- 32 -

Molecular biological studies

The ability of the mutated sodium channel as a whole or through individual alpha subunits to bind known and unknown proteins can be examined. Procedures such as the yeast two-hybrid system are used to discover and identify any functional partners. The principle behind the yeast two-hybrid procedure is that many eukaryotic transcriptional activators, including those in yeast, consist of two discrete modular domains. The first is a DNA-binding domain that binds to a specific promoter sequence and the second is an activation domain that directs the RNA polymerase II complex to transcribe the gene downstream of the DNA binding site. Both domains are required for transcriptional activation as neither domain can activate transcription on its own. In the yeast two-hybrid procedure, the gene of interest or parts thereof (BAIT), is cloned in such a way that it is expressed as a fusion to a peptide that has a DNA binding domain. A second gene, or number of genes, such as those from a cDNA library (TARGET), is cloned so that it is expressed as a fusion to an activation domain. Interaction of the protein of interest with its binding partner brings the DNA-binding peptide together with the activation domain and initiates transcription of the reporter genes. The first reporter gene will select for yeast cells that contain interacting proteins (this reporter is usually a nutritional gene required for growth on selective media). The second reporter is used for confirmation and while being expressed in response to interacting proteins it is usually not required for growth.

The nature of the genes and proteins interacting with the mutant sodium channels can also be studied such that these partners can also be targets for drug discovery.

Structural studies

Recombinant proteins corresponding to mutated sodium channel alpha subunits can be produced in bacterial,

- 33 -

yeast, insect and/or mammalian cells and used in crystallographical and NMR studies. Together with molecular modeling of the protein, structure-driven drug design can be facilitated.

5

Example 5: Generation of polyclonal antibodies against a mutant sodium channel or sodium channel alpha subunit

Following the identification of new mutations in the alpha subunit of the sodium channel in individuals with
10 generalised epilepsy with febrile seizures plus, antibodies can be made to the mutant channel which can selectively bind and distinguish mutant from normal protein. Antibodies specific for mutagenised epitopes are especially useful in cell culture assays to screen for
15 cells which have been treated with pharmaceutical agents to evaluate the therapeutic potential of the agent.

To prepare polyclonal antibodies, short peptides can be designed homologous to a sodium channel subunit amino acid sequence. Such peptides are typically 10 to 15 amino
20 acids in length. These peptides should be designed in regions of least homology to other receptor subunits and should also have poor homology to the mouse orthologue to avoid cross species interactions in further down-stream experiments such as monoclonal antibody production.
25 Synthetic peptides can then be conjugated to biotin (Sulfo-NHS-LC Biotin) using standard protocols supplied with commercially available kits such as the PIERCETM kit (PIERCE). Biotinylated peptides are subsequently complexed with avidin in solution and for each peptide complex, 2
30 rabbits are immunized with 4 doses of antigen (200 ug per dose) in intervals of three weeks between doses. The initial dose is mixed with Freund's Complete adjuvant while subsequent doses are combined with Freund's Immuno-adjuvant. After completion of the immunization, rabbits
35 are test bled and reactivity of sera is assayed by dot blot with serial dilutions of the original peptides. If rabbits show significant reactivity compared with pre-

- 34 -

immune sera, they are then sacrificed and the blood collected such that immune sera can be separated for further experiments.

5 This procedure is repeated to generate antibodies against wild-type forms of receptor subunits. The antibodies specific for mutant sodium channels can subsequently be used to detect the presence and the relative level of the mutant forms in various tissues.

10 Example 6: Generation of monoclonal antibodies against a mutant sodium channel or sodium channel alpha subunit

Monoclonal antibodies can be prepared in the following manner. Immunogen, comprising intact mutated sodium channel or sodium channel alpha subunit peptides, 15 is injected in Freund's adjuvant into mice with each mouse receiving four injections of 10 ug to 100 ug of immunogen. After the fourth injection blood samples taken from the mice are examined for the presence of antibody to the immunogen. Immune mice are sacrificed, their spleens 20 removed and single cell suspensions are prepared (Harlow and Lane, 1988). The spleen cells serve as a source of lymphocytes, which are then fused with a permanently growing myeloma partner cell (Kohler and Milstein, 1975). Cells are plated at a density of 2×10^5 cells/well in 96 25 well plates and individual wells are examined for growth. These wells are then tested for the presence of sodium channel specific antibodies by ELISA or RIA using wild type or mutant subunit target protein. Cells in positive wells are expanded and subcloned to establish and confirm 30 monoclonality. Clones with the desired specificity are expanded and grown as ascites in mice followed by purification using affinity chromatography using Protein A Sepharose, ion-exchange chromatography or variations and combinations of these techniques.

35

Industrial Applicability

The present invention allows for the diagnosis and

- 35 -

treatment of epilepsy or other disorders associated with sodium channel dysfunction, including but not restricted to, malignant hyperthermia, myasthenia, episodic ataxia, neuropathic and inflammatory pain, Alzheimer's disease, 5 Parkinson's disease, schizophrenia, hyperekplexia, myotonias such as hypo- and hyperkalaemic periodic paralysis, paramyotonia congenita and potassium aggravated myotonia as well as cardiac arrhythmias such as long QT syndrome. In particular, the present invention allows for 10 the diagnosis and treatment of generalised epilepsy with febrile seizures plus.

- 36 -

TABLE 1

Comparison of Exon Sizes of SCN1A with Other Human SCNA
5 Subunits

SCN1A		SCN4A		SCN8A		SCN5A	
Exon No.	Exon Size	Exon No.	Exon Size	Exon No.	Exon Size	Exon No.	Exon Size
1A	217	-	-	-	-	1	98
1	313	1	661	1	276	2	324
2	119	2	119	2	121	3	119
3	90	3	90	3	88	4	90
4	129	4	129	4	129	5	129
5	D I	5	92	5	92	6	92
6		6	333	6	222	7	231
7		7	64	7	64	8	64
8		8	142	8	142	9	142
9		9	210	9	207	10	198
10		10A	154	10A	294	11	180
11	C loop1	10B	-	10B	396	12	372
12		10C	-	10C	133	13	133
13		11	239	11	239	14	239
14	D II	12	174	12	174	15	174
15		13	357	13	357	16	351
16		14	477	14	471	17	441
	C loop2					18	162
17		15	136	15	118	19	121
18		16	155	16	155	20	155
19		17	174	17	174	21	174
20	D III	18A	123	18A	123	22	123
21		19	279	19	285	23	282
22		20	54	20	54	24	54
23		21	138	21	138	25	138
24		22	105	22	105	26	105
25	D IV	23	271	23	271	27	271
26		24	>2242	24	>1158	28	3257

Note: D: Transmembrane domain; C: Cytoplasmic loop.

TABLE 2

Primer Sequences Used for Mutation Analysis of SCN1A

Exon	Forward Primer	Reverse Primer	Size (bp)
1A	TACCATAGAGTGAGGCGAGG	ATGGACTTCCTGCTCTGCCC	356
1	CCTCTAGCTCATGTTTCATGAC	TGCAGTAGGCAATTAGCAGC	448
2	CTAATTAAGAAGAGATCCAGTGACAG	GCTATAAAGTGCTTACAGATCATGTAC	356
3	CCCTGAATTTTGGCTAAGCTGCAG	CTACATTAAGACACAGTTTCAAAATCC	263
4	GGGCTACGTTTTCATTTGTATG	GCAACCTATTCTTAAAGCATAAGACTG	355
5	AGGCTCTTTGTACCTACAGC	CATGTAGGGTCCGTCTCATT	199
6	CACACGTGTTAAGTCTTCATAGT	AGCCCCCTCAAGTATTTATCCT	394
7	GAACCTGACCTTCCTGTTCTC	GTTGGCTGTTATCTTCAGTTTC	241
8	GACTAGGCAATATCATAGCATAG	CTTTCTACTATATTATCATCCGG	320
9	TTGAAAGTTGAAGCCACCAC	CCACCTGCTCTTAGGTACTC	363
10	GCCATGCAAATACTTCAGCCC	CACAACAGTGGTTGATTCAGTTG	480
11a	TGAATGCTGAAATCTCCTTCTAC	CTCAGGTTGCTGTTGCGTCTC	306
11b	GATAACGAGAGCCGTAGAGAT	TCTGTAGAAACACTGGCTGG	315
12	CATGAAATTCAGTGTGTCACC	CAGCTCTTGAATTAGACTGTC	347
13a	ATCCTTGGGAGGTTTAGAGT	CATCACAACCAGGTTGACAAC	292
13b	CTGGGACTGTTCTCCATATTG	GCATGAAGGATGGTTGAAAG	277
14	CATTGTGGGAAAATAGCATAAGC	GCTATGCAGAACCCTGATTG	338
15a	TGAGACGGTTAGGGCAGATC	AGAAGTCATTCATGTGCCAGC	348
15b	CTGCAAGATCGCCAGTGATTG	ACATGTGCACAATGTGCAGG	276
16a	GTGGTGTTTCCTTCTCATCAAG	TCTGCTGTATGATTGGACATAC	387
16b	CAACAGTCCTTCATTAGGAAAC	ACCTTCCCACACCTATAGAATC	353
17	CTTGGCAGGCAACTTATTACC	CAAGCTGCACTCCAAATGAAAG	232
18	TGGAAGCAGAGACACTTTATCTAC	GTGCTGTATCACCTTTTCTTAATC	234
19	CCTATTCCAATGAAATGTCATATG	CAAGCTACCTTGAACAGAGAC	318
20	CTACACATTGAATGATGATTCTGT	GCTATATACAATACTTCAGGTTCT	216
21a	ACCAGAGATTACTAGGGGAAT	CCATCGAGCAGTCTCATTTCT	303
21b	ACAACCTGGTGACAGGTTTGAC	CTGGGCTCATAAACTTGTACTAAC	297
22	ACTGTCTTGGTCCAAAATCTG	TTCGATTAATTTTACCACCTGATC	267
23	AGCACCAGTGACATTTCCAAC	GGCAGAGAAAACACTCCAAGG	272
24	GACACAGTTTTAACCAGTTTG	TGTGAGACAAGCATGCAAGTT	207
25	CAGGGCCAATGACTACTTTGC	CTGATTGCTGGGATGATCTTGAATC	477
26a	CGCATGATTTCTTCACTGGTTGG	GCGTAGATGAACATGACTAGG	247
26b	TCCTGCGTTGTTTAACATCGG	ATTCCAACAGATGGGTTCCTCA	288
26c	TGGAAGCTCAGTTAAGGGAGA	AGCGCAGCTGCAAACTGAGAT	261
26d	CCGATGCAACTCAGTTCATGGA	GTAGTGATTGGCTGATAGGAG	274
26e	AGAGCGATTCATGGCTTCCAATCC	TGCCTTCTTGCTCATGTTTTTCCACA	335
26f	CCTATGACCGGGTGACAAAGCC	TGCTGACAAGGGGTCACTGTCT	242

5 Note: Primer sequences are listed 5' to 3'. Due to the large size of exons 11, 13, 15, 16, 21 and 26, the exons were split into two or more overlapping amplicons.

5

TABLE 3

SCN1A Polymorphisms Identified

SCN1A polymorphism			Frequency (%)	
Position	Mutation	Amino Acid Change	GEFS+	Normal
Intron 13	IVS13-37C>A	-	2.4	8.6
Exon 14	c.2522C>G	-	2.4	8.6
Intron 15	IVS15+54A>G	-	36.3	23.6
Exon 15	c.2889T>C	-	1.2	0.0
Exon 16	c.3199G>A	T1067A	29.5	30.8
Exon 26	c.5782C>G	R1928G	1.2	1.7

Note: Total GEFS+ samples = 53; Total normal samples=60.

77748-6

- 39 -

References

References cited herein are listed on the following pages.

- 5 Baulac S. et al. (1999). *Am. J. Hum. Genet.* 65: 1078-1085.
- Bendahhou S. et al. (1999). *J. Neurosci.* 19: 4762-4771.
- Cole, SP. et al. (1984). *Mol. Cell Biol.* 62: 109-120.
- Cote, RJ. et al. (1983). *Proc. Natl. Acad. Sci. USA* 80: 2026-2030.
- 10 Escayg A. et al. (2000). *Nature Genet.* 24: 343-345.
- Goldman, CK. et al. (1997). *Nature Biotechnology* 15: 462-466.
- Harlow, E. and Lane, D. (1988). *Antibodies: A Laboratory Manual* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).
- 15 Heller, RA. et al. (1997). *Proc. Natl. Acad. Sci. USA* 94: 2150-2155.
- Huse, WD. et al. (1989). *Science* 246: 1275-1281.
- Kohler, G. and Milstein, C. (1975). *Nature* 256: 495-497.
- 20 Kozbor, D. et al. (1985). *J. Immunol. Methods* 81:31-42.
- Kuhn, FJP. and Greeff, NG. (1996). *J. Gen. Physiol.* 114: 167-183.
- Lopes-Cendes I. et al. (2000). *Am. J. Hum. Genet.* 66: 698-701.
- 25 Moulard B. et al. (1999). *Am. J. Hum. Genet.* 65: 1396-1400.
- Orlandi, R. et al. (1989). *Proc. Natl. Acad. Sci. USA* 86: 3833-3837.
- Peiffer A. et al. (1999). *Ann. Neurol.* 46: 671-678.
- 30 Plummer NW. et al. (1998). *Genomics* 54: 287-296.
- Plummer NW. and Meisler MH. (1999). *Genomics* 57: 323-331.
- Sambrook, J. et al. (1989). *Molecular cloning : a laboratory manual. Second Edition.* (Cold Spring Harbour Laboratory Press, New York).
- 35 Scharf, D. et al. (1994). *Results Probl. Cell Differ.* 20: 125-162.
- Scheffer IE. and Berkovic SF. (1997). *Brain* 120: 479-490.

- 40 -

- Scheffer IE. et al. (2000). *Ann. Neurol.* 47: 840-841.
- Schena, M. et al. (1996). *Proc. Natl. Acad. Sci. USA* 93: 10614-10619.
- Singh R. et al. (1999). *Ann Neurol.* 45: 75-81.
- 5 Wallace RH. et al. (1998). *Nature Genet.* 19: 366-370.
- Winter, G. et al. (1991). *Nature* 349: 293-299.

SEQUENCE LISTING

<110> Bionomics Limited

<120> Mutations in neuronal gene sodium-channel alpha1-subunit and their polypeptides and their treatment of generalized epilepsy with febrile seizures plus

<130> New SCN1A Mutations

<160> 89

<170> PatentIn version 3.1

<210> 1

<211> 8381

<212> DNA

<213> Homo sapiens

<400> 1

atactgcaga	ggtctctggt	gcatgtgtgt	atgtgtgctg	ttgtgtgtgt	ttgtgtgtct	60
gtgtgttctg	ccccagttag	actgcagccc	ttgtaaatac	tttgacacct	tttgcaagaa	120
ggaatctgaa	caattgcaac	tgaaggcaca	ttgttatcat	ctcgtctttg	ggtgatgctg	180
ttcctcactg	cagatggata	atcttccttt	taatcaggaa	tttcatatgc	agaataaatg	240
gtaattaaaa	tgtgcaggat	gacaagatgg	agcaaacagt	gcttgtagca	ccaggacctg	300
acagcttcaa	cttcttcacc	agagaatctc	ttgcggctat	tgaaagacgc	attgcagaag	360
aaaaggcaaa	gaatcccaaa	ccagacaaaa	aagatgacga	cgaaaatggc	ccaaagccaa	420
atagtgaact	ggaagctgga	aagaaccttc	catttattta	tggagacatt	cctccagaga	480
tggtgtcaga	gcccctggag	gacctggacc	cctactatat	caataagaaa	actttttatg	540
tattgaataa	attgaaggcc	atcttccggt	tcagtgccac	ctctgccctg	tacattttta	600
ctcccttcaa	tcctcttagg	aaaatagcta	ttaagatttt	ggtacattca	ttattcagca	660
tgctaattat	gtgcactatt	ttgacaaaact	gtgtgtttat	gacaatgagt	aacctctctg	720
attggacaaa	gaatgtagaa	tacaccttca	caggaatata	tacttttgaa	tcacttataa	780
aaattattgc	aaggggattc	tgtttagaag	atcttacttt	ccttcggggt	ccatggaact	840
ggctcgattt	cactgtcatt	acatttgcgt	acgtcacaga	gtttgtggac	ctgggcaatg	900
tctcggcatt	gagaacattc	agagttctcc	gagcattgaa	gacgatttca	gtcattccag	960
gcctgaaaac	cattgtggga	gccctgatcc	agtctgtgaa	gaagctctca	gatgtaatga	1020
tcctgactgt	gttctgtctg	agcgtatttg	ctctaattgg	gctgcagctg	ttcatgggca	1080
acctgaggaa	taaatgtata	caatggcctc	ccaccaatgc	ttccttggag	gaacatagta	1140
tagaaaagaa	tataactgtg	aattataatg	gtacacttat	aaatgaaact	gtctttgagt	1200
ttgactggaa	gtcatatatt	caagattcaa	gatataatta	tttcctggag	ggttttttag	1260
atgcactact	atgtggaaat	agctctgatg	caggccaatg	tccagaggga	tatatgtgtg	1320
tgaaagctgg	tagaaatccc	aattatggct	acacaagctt	tgataccttc	agttgggctt	1380
ttttgtcctt	gtttcgacta	atgactcagg	acttctggga	aaatctttat	caactgacat	1440
tacgtgctgc	tgggaaaacg	tacatgatat	tttttgtatt	ggtcattttc	ttgggctcat	1500
tctacctaat	aaatttgatc	ctggctgtgg	tggccatggc	ctacgaggaa	cagaatcagg	1560
ccaccttgga	agaagcagaa	cagaaagagg	ccgaatttca	gcagatgatt	gaacagctta	1620
aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcttcagaa	cattccagag	1680
agcccagtgc	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgtctt	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctgggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aaggttttcg	cttctccatt	gaagggaacc	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atccgtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagcttttaga	gggagagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtggt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtgggtt	2220
ccttggttgg	tggaccttca	gttcctacat	cgctgttggg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaagggtcaag	ttctttccac	gtttccatgg	acttttctaga	agatccttcc	caaaggcaac	2400

gagcaatgag	tatagccagc	attctaacaa	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgcc	accctgttgg	tataaatatt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattggtt	aaaagtga	catgttgtca	acctgggtgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaaata	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggtttttact	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggtttt	attgtgacgc	ttagcctggg	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaataatg	ctaataaaga	tcacgggcaa	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcatttttgc	cgtgggtcggc	atgcagctct	3000
ttggtaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtgtt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcatgatggg	catgggtgatt	ggaaacctag	tggtcctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgag	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aattttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaattgaa	ctacaagtgg	tatagggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagtctta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaattttaaac	acggaagact	3660
ttagtagtga	atcggtctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaaatatgc	tgacaagggtt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tatttcacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaatctct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggg	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatattctgg	ctaattttca	gcacatggg	cgtaaatttg	tttgctggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attgggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttgagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatggtctt	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctattttac	tggagagtgt	gtactgaaac	5040
tcattctctc	acgccattat	tattttacca	ttggatggaa	tatttttgat	tttgtggttg	5100
tcattctctc	cattgtaggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160
ctaccctgtt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaagg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttctc	gcgttgttta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcattctacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggagcg	atgacatggt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgaactgtg	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttcct	ggttgtgggtg	aacatgtaca	tgcggtcat	cctggagaac	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgaggttt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcattggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaaccaa	caaactccag	ctcattgcca	5820
tggatttgcc	catgggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaagggtct	cctatcagcc	aatcactact	actttaaaac	6000

```

gaaaacaaga ggaagtatct gctgtcatta ttcagcgtgc ttacagacgc caccttttaa 6060
agcgaactgt aaaacaagct tcctttacgt acaataaaaa caaaatcaaa ggtggggcta 6120
atcttcttat aaaagaagac atgataattg acagaataaa tgaaaactct attacagaaa 6180
aaactgatct gaccatgtcc actgcagctt gtccaccttc ctatgaccgg gtgacaaagc 6240
caattgtgga aaaacatgag caagaaggca aagatgaaaa agccaaaggg aaataaatga 6300
aaataaataa aaataattgg gtgacaaatt gtttacagcc tgtgaagggtg atgtattttt 6360
atcaacagga ctcttttagg aggtcaatgc caaactgact gtttttacac aaatctcctt 6420
aaggtcagtg cctacaataa gacagtgacc ccttgtcagc aaactgtgac tctgtgtaaa 6480
ggggagatga ccttgacagg aggttactgt tctcactacc agctgacact gctgaagata 6540
agatgcacaa tggctagtca gactgtaggg accagtttca aggggtgcaa acctgtgatt 6600
ttgggggtgt ttaacatgaa acactttagt gtagtaattg tatccactgt ttgcatttca 6660
actgccacat ttgtcacatt tttatggaat ctgttagtgg attcatcttt ttgttaatcc 6720
atgtgtttat tatatgtgac tattttttgta aacgaagttt ctgttgagaa ataggctaag 6780
gacctctata acaggatgac cacctggggg gtatggcaac cacatggccc tcccagctac 6840
acaaagtcgt ggtttgcatg agggcatgct gcacttagag atcatgcatg agaaaaagtc 6900
acaagaaaaa caaattctta aatttcacca tatttctggg aggggtaatt ggggtgataag 6960
tggaggtgct ttgttgatct tgttttgca aatccagccc ctagaccaag tagattattt 7020
gtgggtaggc cagtaaatct tagcagggtgc aaacttcatt caaatgtttg gagtcataaa 7080
tgttatgttt ctttttgttg tattaataaaa aaaacctgaa tagtgaatat tgcccctcac 7140
cctccaccgc cagaagactg aattgaccaa aattactctt tataaatttc tgctttttcc 7200
tgcactttgt ttagccatct ttgggctctc agcaagggtg aactgtata tgtaaatgaa 7260
atgctattta ttatgtaaat agtcatttta ccctgtggtg cacgtttgag caaacaataa 7320
atgacctaag cacagtattt attgcatcaa atatgtacca caagaaatgt agagtgaag 7380
ctttacacag gtaataaaat gtattctgta ccatttatag atagtttgga tgctatcaat 7440
gcatgtttat attaccatgc tgctgtatct ggtttctctc actgctcaga atctcattta 7500
tgagaaacca tatgtcagtg gtaaagtcaa ggaaattgtt caacagatct catttattta 7560
agtcattaag caatagtttg cagcacttta acagcttttt ggttattttt acattttaag 7620
tggaatacat atggtatata gccagactgt acagacatgt ttaaaaaaac acactgctta 7680
acctattaaa tatgtgttta gaattttata agcaaatata aatactgtaa aaagtcactt 7740
tattttattt ttcagcatta tgtacataaa tatgaagagg aaattatctt caggttgata 7800
tcacaatcac ttttcttact ttctgtccat agtacttttt catgaaagaa atttgctaaa 7860
taagacatga aaacaagact gggtagttgt agatttctgc tttttaaatt acatttgcta 7920
attttagatt atttcacaat tttaaggagc aaaatagggt cacgattcat atccaaatta 7980
tgctttgcaa ttggaaaagg gtttaaaatt ttatttatat ttctggtagt acctgtacta 8040
actgaattga aggtagtgtt tatgttattt ttgttctttt tttctgactt cggtttatgt 8100
tttcatttct ttggagtaat gctgctctag attgttctaa atagaatgtg ggcttcataa 8160
tttttttttc caaaaaaca gagtagtcaa cttatatagt caattacatc aggacatttt 8220
gtgtttctta cagaagcaaa ccataggctc ctcttttcct taaaactact tagataaact 8280
gtattcgtga actgcatgct ggaaaatgct actattatgc taaataatgc taaccaacat 8340
ttaaaatgtg caaaactaat aaagattaca ttttttattt t 8381

```

<210> 2
 <211> 2009
 <212> PRT
 <213> Homo sapiens

<400> 2
 Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe
 1 5 10 15
 Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu
 20 25 30
 Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly
 35 40 45
 Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
 50 55 60
 Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
 65 70 75 80

Tyr	Glu	Lys	Arg	Tyr	Ser	Ser	Pro	His	Gln	Ser	Leu	Leu	Ser	Ile	Arg		
545					550					555					560		
Gly	Ser	Leu	Phe	Ser	Pro	Arg	Arg	Asn	Ser	Arg	Thr	Ser	Leu	Phe	Ser		
				565					570					575			
Phe	Arg	Gly	Arg	Ala	Lys	Asp	Val	Gly	Ser	Glu	Asn	Asp	Phe	Ala	Asp		
			580					585					590				
Asp	Glu	His	Ser	Thr	Phe	Glu	Asp	Asn	Glu	Ser	Arg	Arg	Asp	Ser	Leu		
	595					600						605					
Phe	Val	Pro	Arg	Arg	His	Gly	Glu	Arg	Arg	Asn	Ser	Asn	Leu	Ser	Gln		
	610					615						620					
Thr	Ser	Arg	Ser	Ser	Arg	Met	Leu	Ala	Val	Phe	Pro	Ala	Asn	Gly	Lys		
625					630					635					640		
Met	His	Ser	Thr	Val	Asp	Cys	Asn	Gly	Val	Val	Ser	Leu	Val	Gly	Gly		
				645				650						655			
Pro	Ser	Val	Pro	Thr	Ser	Pro	Val	Gly	Gln	Leu	Leu	Pro	Glu	Val	Ile		
			660					665					670				
Ile	Asp	Lys	Pro	Ala	Thr	Asp	Asp	Asn	Gly	Thr	Thr	Thr	Glu	Thr	Glu		
	675					680						685					
Met	Arg	Lys	Arg	Arg	Ser	Ser	Ser	Phe	His	Val	Ser	Met	Asp	Phe	Leu		
	690				695						700						
Glu	Asp	Pro	Ser	Gln	Arg	Gln	Arg	Ala	Met	Ser	Ile	Ala	Ser	Ile	Leu		
705				710						715					720		
Thr	Asn	Thr	Val	Glu	Glu	Leu	Glu	Glu	Ser	Arg	Gln	Lys	Cys	Pro	Pro		
			725					730						735			
Cys	Trp	Tyr	Lys	Phe	Ser	Asn	Ile	Phe	Leu	Ile	Trp	Asp	Cys	Ser	Pro		
			740					745					750				
Tyr	Trp	Leu	Lys	Val	Lys	His	Val	Val	Asn	Leu	Val	Val	Met	Asp	Pro		
	755					760						765					
Phe	Val	Asp	Leu	Ala	Ile	Thr	Ile	Cys	Ile	Val	Leu	Asn	Thr	Leu	Phe		
	770					775						780					
Met	Ala	Met	Glu	His	Tyr	Pro	Met	Thr	Asp	His	Phe	Asn	Asn	Val	Leu		
785				790					795						800		
Thr	Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Phe		
			805					810					815				
Leu	Lys	Ile	Ile	Ala	Met	Asp	Pro	Tyr	Tyr	Tyr	Phe	Gln	Glu	Gly	Trp		
			820					825					830				
Asn	Ile	Phe	Asp	Gly	Phe	Ile	Val	Thr	Leu	Ser	Leu	Val	Glu	Leu	Gly		
	835						840						845				
Leu	Ala	Asn	Val	Glu	Gly	Leu	Ser	Val	Leu	Arg	Ser	Phe	Arg	Leu	Leu		
	850					855					860						
Arg	Val	Phe	Lys	Leu	Ala	Lys	Ser	Trp	Pro	Thr	Leu	Asn	Met	Leu	Ile		
865				870						875					880		
Lys	Ile	Ile	Gly	Asn	Ser	Val	Gly	Ala	Leu	Gly	Asn	Leu	Thr	Leu	Val		
			885					890						895			
Leu	Ala	Ile	Ile	Val	Phe	Ile	Phe	Ala	Val	Val	Gly	Met	Gln	Leu	Phe		
			900					905					910				
Gly	Lys	Ser	Tyr	Lys	Asp	Cys	Val	Cys	Lys	Ile	Ala	Ser	Asp	Cys	Gln		
	915						920						925				
Leu	Pro	Arg	Trp	His	Met	Asn	Asp	Phe	Phe	His	Ser	Phe	Leu	Ile	Val		
	930					935						940					
Phe	Arg	Val	Leu	Cys	Gly	Glu	Trp	Ile	Glu	Thr	Met	Trp	Asp	Cys	Met		
945				950						955					960		
Glu	Val	Ala	Gly	Gln	Ala	Met	Cys	Leu	Thr	Val	Phe	Met	Met	Val	Met		
			965						970					975			
Val	Ile	Gly	Asn	Leu	Val	Val	Leu	Asn	Leu	Phe	Leu	Ala	Leu	Leu	Leu		
			980					985					990				
Ser	Ser	Phe	Ser	Ala	Asp	Asn	Leu	Ala	Ala	Thr	Asp	Asp	Asp	Asn	Glu		
		995					1000						1005				

Met	Asn	Asn	Leu	Gln	Ile	Ala	Val	Asp	Arg	Met	His	Lys	Gly	Val
1010						1015					1020			
Ala	Tyr	Val	Lys	Arg	Lys	Ile	Tyr	Glu	Phe	Ile	Gln	Gln	Ser	Phe
1025						1030					1035			
Ile	Arg	Lys	Gln	Lys	Ile	Leu	Asp	Glu	Ile	Lys	Pro	Leu	Asp	Asp
1040						1045					1050			
Leu	Asn	Asn	Lys	Lys	Asp	Ser	Cys	Met	Ser	Asn	His	Thr	Thr	Glu
1055						1060					1065			
Ile	Gly	Lys	Asp	Leu	Asp	Tyr	Leu	Lys	Asp	Val	Asn	Gly	Thr	Thr
1070						1075					1080			
Ser	Gly	Ile	Gly	Thr	Gly	Ser	Ser	Val	Glu	Lys	Tyr	Ile	Ile	Asp
1085						1090					1095			
Glu	Ser	Asp	Tyr	Met	Ser	Phe	Ile	Asn	Asn	Pro	Ser	Leu	Thr	Val
1100						1105					1110			
Thr	Val	Pro	Ile	Ala	Val	Gly	Glu	Ser	Asp	Phe	Glu	Asn	Leu	Asn
1115						1120					1125			
Thr	Glu	Asp	Phe	Ser	Ser	Glu	Ser	Asp	Leu	Glu	Glu	Ser	Lys	Glu
1130						1135					1140			
Lys	Leu	Asn	Glu	Ser	Ser	Ser	Ser	Ser	Glu	Gly	Ser	Thr	Val	Asp
1145						1150					1155			
Ile	Gly	Ala	Pro	Val	Glu	Glu	Gln	Pro	Val	Val	Glu	Pro	Glu	Glu
1160						1165					1170			
Thr	Leu	Glu	Pro	Glu	Ala	Cys	Phe	Thr	Glu	Gly	Cys	Val	Gln	Arg
1175						1180					1185			
Phe	Lys	Cys	Cys	Gln	Ile	Asn	Val	Glu	Glu	Gly	Arg	Gly	Lys	Gln
1190						1195					1200			
Trp	Trp	Asn	Leu	Arg	Arg	Thr	Cys	Phe	Arg	Ile	Val	Glu	His	Asn
1205						1210					1215			
Trp	Phe	Glu	Thr	Phe	Ile	Val	Phe	Met	Ile	Leu	Leu	Ser	Ser	Gly
1220						1225					1230			
Ala	Leu	Ala	Phe	Glu	Asp	Ile	Tyr	Ile	Asp	Gln	Arg	Lys	Thr	Ile
1235						1240					1245			
Lys	Thr	Met	Leu	Glu	Tyr	Ala	Asp	Lys	Val	Phe	Thr	Tyr	Ile	Phe
1250						1255					1260			
Ile	Leu	Glu	Met	Leu	Leu	Lys	Trp	Val	Ala	Tyr	Gly	Tyr	Gln	Thr
1265						1270					1275			
Tyr	Phe	Thr	Asn	Ala	Trp	Cys	Trp	Leu	Asp	Phe	Leu	Ile	Val	Asp
1280						1285					1290			
Val	Ser	Leu	Val	Ser	Leu	Thr	Ala	Asn	Ala	Leu	Gly	Tyr	Ser	Glu
1295						1300					1305			
Leu	Gly	Ala	Ile	Lys	Ser	Leu	Arg	Thr	Leu	Arg	Ala	Leu	Arg	Pro
1310						1315					1320			
Leu	Arg	Ala	Leu	Ser	Arg	Phe	Glu	Gly	Met	Arg	Val	Val	Val	Asn
1325						1330					1335			
Ala	Leu	Leu	Gly	Ala	Ile	Pro	Ser	Ile	Met	Asn	Val	Leu	Leu	Val
1340						1345					1350			
Cys	Leu	Ile	Phe	Trp	Leu	Ile	Phe	Ser	Ile	Met	Gly	Val	Asn	Leu
1355						1360					1365			
Phe	Ala	Gly	Lys	Phe	Tyr	His	Cys	Ile	Asn	Thr	Thr	Thr	Gly	Asp
1370						1375					1380			
Arg	Phe	Asp	Ile	Glu	Asp	Val	Asn	Asn	His	Thr	Asp	Cys	Leu	Lys
1385						1390					1395			
Leu	Ile	Glu	Arg	Asn	Glu	Thr	Ala	Arg	Trp	Lys	Asn	Val	Lys	Val
1400						1405					1410			
Asn	Phe	Asp	Asn	Val	Gly	Phe	Gly	Tyr	Leu	Ser	Leu	Leu	Gln	Val
1415						1420					1425			
Ala	Thr	Phe	Lys	Gly	Trp	Met	Asp	Ile	Met	Tyr	Ala	Ala	Val	Asp
1430						1435					1440			

Ser	Arg	Asn	Val	Glu	Leu	Gln	Pro	Lys	Tyr	Glu	Lys	Ser	Leu	Tyr
1445						1450					1455			
Met	Tyr	Leu	Tyr	Phe	Val	Ile	Phe	Ile	Ile	Phe	Gly	Ser	Phe	Phe
1460						1465					1470			
Thr	Leu	Asn	Leu	Phe	Ile	Gly	Val	Ile	Ile	Asp	Asn	Phe	Asn	Gln
1475						1480					1485			
Gln	Lys	Lys	Lys	Phe	Gly	Gly	Gln	Asp	Ile	Phe	Met	Thr	Glu	Glu
1490						1495					1500			
Gln	Lys	Lys	Tyr	Tyr	Asn	Ala	Met	Lys	Lys	Leu	Gly	Ser	Lys	Lys
1505						1510					1515			
Pro	Gln	Lys	Pro	Ile	Pro	Arg	Pro	Gly	Asn	Lys	Phe	Gln	Gly	Met
1520						1525					1530			
Val	Phe	Asp	Phe	Val	Thr	Arg	Gln	Val	Phe	Asp	Ile	Ser	Ile	Met
1535						1540					1545			
Ile	Leu	Ile	Cys	Leu	Asn	Met	Val	Thr	Met	Met	Val	Glu	Thr	Asp
1550						1555					1560			
Asp	Gln	Ser	Glu	Tyr	Val	Thr	Thr	Ile	Leu	Ser	Arg	Ile	Asn	Leu
1565						1570					1575			
Val	Phe	Ile	Val	Leu	Phe	Thr	Gly	Glu	Cys	Val	Leu	Lys	Leu	Ile
1580						1585					1590			
Ser	Leu	Arg	His	Tyr	Tyr	Phe	Thr	Ile	Gly	Trp	Asn	Ile	Phe	Asp
1595						1600					1605			
Phe	Val	Val	Val	Ile	Leu	Ser	Ile	Val	Gly	Met	Phe	Leu	Ala	Glu
1610						1615					1620			
Leu	Ile	Glu	Lys	Tyr	Phe	Val	Ser	Pro	Thr	Leu	Phe	Arg	Val	Ile
1625						1630					1635			
Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Lys	Gly	Ala
1640						1645					1650			
Lys	Gly	Ile	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser	Leu	Pro
1655						1660					1665			
Ala	Leu	Phe	Asn	Ile	Gly	Leu	Leu	Leu	Phe	Leu	Val	Met	Phe	Ile
1670						1675					1680			
Tyr	Ala	Ile	Phe	Gly	Met	Ser	Asn	Phe	Ala	Tyr	Val	Lys	Arg	Glu
1685						1690					1695			
Val	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Glu	Thr	Phe	Gly	Asn	Ser
1700						1705					1710			
Met	Ile	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp	Asp	Gly
1715						1720					1725			
Leu	Leu	Ala	Pro	Ile	Leu	Asn	Ser	Lys	Pro	Pro	Asp	Cys	Asp	Pro
1730						1735					1740			
Asn	Lys	Val	Asn	Pro	Gly	Ser	Ser	Val	Lys	Gly	Asp	Cys	Gly	Asn
1745						1750					1755			
Pro	Ser	Val	Gly	Ile	Phe	Phe	Phe	Val	Ser	Tyr	Ile	Ile	Ile	Ser
1760						1765					1770			
Phe	Leu	Val	Val	Val	Asn	Met	Tyr	Ile	Ala	Val	Ile	Leu	Glu	Asn
1775						1780					1785			
Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Ala	Glu	Pro	Leu	Ser	Glu	Asp
1790						1795					1800			
Asp	Phe	Glu	Met	Phe	Tyr	Glu	Val	Trp	Glu	Lys	Phe	Asp	Pro	Asp
1805						1810					1815			
Ala	Thr	Gln	Phe	Met	Glu	Phe	Glu	Lys	Leu	Ser	Gln	Phe	Ala	Ala
1820						1825					1830			
Ala	Leu	Glu	Pro	Pro	Leu	Asn	Leu	Pro	Gln	Pro	Asn	Lys	Leu	Gln
1835						1840					1845			
Leu	Ile	Ala	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile	His
1850						1855					1860			
Cys	Leu	Asp	Ile	Leu	Phe	Ala	Phe	Thr	Lys	Arg	Val	Leu	Gly	Glu
1865						1870					1875			

Ser	Gly	Glu	Met	Asp	Ala	Leu	Arg	Ile	Gln	Met	Glu	Glu	Arg	Phe
1880						1885					1890			
Met	Ala	Ser	Asn	Pro	Ser	Lys	Val	Ser	Tyr	Gln	Pro	Ile	Thr	Thr
1895						1900					1905			
Thr	Leu	Lys	Arg	Lys	Gln	Glu	Glu	Val	Ser	Ala	Val	Ile	Ile	Gln
1910						1915					1920			
Arg	Ala	Tyr	Arg	Arg	His	Leu	Leu	Lys	Arg	Thr	Val	Lys	Gln	Ala
1925						1930					1935			
Ser	Phe	Thr	Tyr	Asn	Lys	Asn	Lys	Ile	Lys	Gly	Gly	Ala	Asn	Leu
1940						1945					1950			
Leu	Ile	Lys	Glu	Asp	Met	Ile	Ile	Asp	Arg	Ile	Asn	Glu	Asn	Ser
1955						1960					1965			
Ile	Thr	Glu	Lys	Thr	Asp	Leu	Thr	Met	Ser	Thr	Ala	Ala	Cys	Pro
1970						1975					1980			
Pro	Ser	Tyr	Asp	Arg	Val	Thr	Lys	Pro	Ile	Val	Glu	Lys	His	Glu
1985						1990					1995			
Gln	Glu	Gly	Lys	Asp	Glu	Lys	Ala	Lys	Gly	Lys				
2000						2005								

<210> 3
 <211> 8381
 <212> DNA
 <213> Homo sapiens

<400> 3
 atactgcaga ggtctctggt gcatgtgtgt atgtgtgcgt ttgtgtgtgt ttgtgtgtct 60
 gtgtgttctg cccagtgag actgcagccc ttgtaaatac tttgacacct tttgcaagaa 120
 ggaatctgaa caattgcaac tgaaggcaca ttgttatcat ctctcttttg ggtgatgctg 180
 ttcctcactg cagatggata attttccttt taatcaggaa tttcatatgc agaataaatg 240
 gtaattaaaa tgtgcaggat gacaagatgg agcaaacagt gcttgtacca ccaggacctg 300
 acagcttcaa cttcttcacc agagaatctc ttgcggctat tgaaagacgc attgcagaag 360
 aaaaggcaaa gaatcccaaa ccagacaaaa aagatgacga cgaaaatggc ccaaagccaa 420
 atagtgactt ggaagctgga aagaaccttc catttattta tggagacatt cctccagaga 480
 tgggtgtcaga gccctggag gacctggacc cctactatat caataagaaa acttttatag 540
 tattgaataa attgaaggcc atcttccggt tcagtgccac ctctgccctg tacattttaa 600
 ctcccttcaa tcctcttagg aaaatagcta ttaagatttt ggtacattca ttattcagca 660
 tgctaattat gtgcactatt ttgacaaact gtgtgtttat gacaatgagt aaccctcctg 720
 attggacaaa gaatgtagaa tacaccttca caggaatata tacttttgaa tcacttataa 780
 aaattattgc aaggggattc tgtttagaag attttacttt ccttcgggat ccatggaact 840
 ggctcgattt cactgtcatt acatttgcgt acgtcacaga gtttgtggac ctgggcaatg 900
 tctcggcatt gagaacattc agagtctctc gagcattgaa gacgatttca gtcattccag 960
 gcctgaaaac cattgtggga gccctgatcc agtctgtgaa gaagctctca gatgtaatga 1020
 tcctgactgt gttctgtctg agcgtatttg ctctaattgg gctgcagctg ttcattgggca 1080
 acctgaggaa taaatgtata caatggcctc ccaccaatgc ttccttggag gaacatagta 1140
 tagaaaagaa tataactgtg aattataatg gtacacttat aaatgaaact gtctttgagt 1200
 ttgactggaa gtcatatatt caagattcaa gatatcatta tttcctggag ggtttttttag 1260
 atgcactact atgtggaaat agctctgatg caggccaatg tccagaggga tatatgtgtg 1320
 tgaaagctgg tagaaatccc aattatggct acacaagctt tgataccttc agttgggctt 1380
 ttttgtcctt gtttcgacta atgactcagg acttctggga aaatctttat caactgacat 1440
 tacgtgctgc tgggaaaacg tacatgatat tttttgtatt ggtcattttc ttgggctcat 1500
 tctacctaataa aaatttgatc ctggctgtgg tggccatggc ctacgaggaa cagaatcagg 1560
 ccaccttggga agaagcagaa cagaaagagg ccgaatttca gcagatgatt gaacagctta 1620
 aaaagcaaca ggaggcagct cagcaggcag caacggcaac tgcctcagaa cattccagag 1680
 agcccagtgct agcaggcagg ctctcagaca gctcatctga agcctctaag ttgagttcca 1740
 agagtgtctaa ggaaagaaga aatcggagga agaaaagaaa acagaaagag cagtctggtg 1800
 gggaagagaa agatgaggat gaattccaaa aatctgaatc tgaggacagc atcaggagga 1860
 aagggttttcg cttctccatt gaagggaacc gattgacata tgaaaagagg tactcctccc 1920
 cacaccagtc tttgttgagc atccgtggct ccctattttc accaaggcga aatagcagaa 1980

caagcctttt	cagcttttaga	gggcgagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtgtt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtgggtt	2220
ccttggttgg	tggaccttca	gttcctacat	cgctgtttgg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaaggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacia	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttgg	tataaatttt	ccaacatatt	cttaatctgg	gactgtttctc	2520
catattgggt	aaaagtgaia	catgttgtca	acctggttgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaata	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttcact	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggttt	attgtgacgc	ttagcctggg	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgtttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaataatg	ctaataaaga	tcacggcaa	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcattttttgc	cgtgggtcggc	atgcagctct	3000
ttggtaaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtgtt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcatgatggg	catggtgatt	ggaaacctag	tggctcctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgacagc	aaccttgacg	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aattttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagtctta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaatttaaac	acggaagact	3660
ttagtagtga	atcggtatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tgggttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtgggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaaatatgc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tattttacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaactctct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggg	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tgctttgtct	tatattctgg	ctaattttca	gcatcatggg	cgtaaatttg	tttgctggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatggtctt	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atgggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctattttac	tggagagtgt	gtactgaaac	5040
tcactctctct	acgccattat	tattttacca	ttggatggaa	tatttttgat	tttgtggttg	5100
tcattctctc	cattgtagggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160
ctaccctgtt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttcct	gcgttgttta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcactctacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatgtt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgactgtg	accctaataa	agttaaccct	ggaagctcag	5520

```

ttaagggaga ctgtgggaac ccattctgttg gaatttttctt ttttgtcagt tacatcatca 5580
tattccttcct gggtgtggtg aacatgtaca tcgcgggtcat cctgggagaac ttcagtgttg 5640
ctactgaaga aagtgcagag cctctgagtg aggatgactt tgagatgttc tatgagggtt 5700
gggagaagtt tgatcccgat gcaactcagt tcatggaatt tgaaaaatta tctcagtttg 5760
cagctgcgct tgaaccgcct ctcaatctgc cacaaccaaa caaactccag ctcattgcca 5820
tggattttgcc catggtgagt ggtgaccgga tccactgtct tgatatctta tttgctttta 5880
caaagcgggt tctaggagag agtggagaga tggatgctct acgaatacag atggaagagc 5940
gattcatggc ttccaatcct tccaaggctc cctatcagcc aatcactact actttaaaac 6000
gaaaacaaga ggaagtatct gctgtcatta ttcagcgtgc ttacagacgc caccttttaa 6060
agcgaactgt aaaacaagct tccttttacgt acaataaaaa caaaatcaaa ggtggggcta 6120
atcttcttat aaaagaagac atgataattg acagaataaa tgaaaactct attacagaaa 6180
aaactgatct gaccatgtcc actgcagctt gtccaccttc ctatgaccgg gtgacaaagc 6240
caattgtgga aaaacatgag caagaaggca aagatgaaaa agccaaaggg aaataaatga 6300
aaataaataa aaataattgg gtgacaaatt gtttacagcc tgtgaagggtg atgtattttt 6360
atcaacagga ctcttttagg aggtcaatgc caaactgact gtttttacac aaatctcctt 6420
aaggtcagtg cctacaataa gacagtgacc ccttgtcagc aaactgtgac tctgtgtaaa 6480
ggggagatga ccttgacagg aggttactgt tctcactacc agctgacact gctgaagata 6540
agatgcacaa tggctagtca gactgtaggg accagtttca aggggtgcaa acctgtgatt 6600
ttggggttgt ttaacatgaa acactttagt gtagtaattg tatccactgt ttgcatttca 6660
actgccacat ttgtcacatt tttatggaat ctgttagtgg attcatcttt ttgttaatcc 6720
atgtgtttat tatatgtgac tattttttgta aacgaagttt ctgttgagaa ataggctaag 6780
gacctctata acaggatgac cacctggggg gtatggcaac cacatggccc tcccagctac 6840
acaaagtcgt gggttgcatg agggcatgct gcacttagag atcatgcatg agaaaaagtc 6900
acaagaaaaa caaattctta aatttcacca tatttctggg aggggttaatt gggtgataag 6960
tgagggtgct ttgttgatct tggtttgcca aatccagccc ctagaccaag tagattattt 7020
gtgggtaggc cagtaaatct tagcagggtgc aaacttcatt caaatgtttg gagtcataaa 7080
tgttatgttt ctttttggtg tattaaaaaa aaaacctgaa tagtgaatat tgcccctcac 7140
cctccaccgc cagaagactg aattgaccaa aattactctt tataaatttc tgctttttcc 7200
tgcactttgt ttagccatct ttgggctctc agcaagggtg aactgtata tgtaaatgaa 7260
atgctattta ttatgtaaat agtcatttta ccctgtggtg cacgtttgag caaacaataa 7320
atgacctaag cacagtattt attgcatcaa atatgtacca caagaaatgt agagtgcagg 7380
ctttacacag gtaataaaat gtattctgta ccatttatag atagtttgga tgctatcaat 7440
gcatgtttat attaccatgc tgctgtatct gggttctctc actgctcaga atctcattta 7500
tgagaaacca tatgtcagtg gtaaagtcaa ggaaattgtt caacagatct catttattta 7560
agtcattaag caatagtttg cagcacttta acagcttttt gggtattttt acattttaag 7620
tgataacat atggtatata gccagactgt acagacatgt ttaaaaaaac acactgctta 7680
acctattaaa tatgtgttta gaattttata agcaaataa aatactgtaa aaagtcactt 7740
tattttatatt ttcagcatta tgtacataaa tatgaagagg aaattatctt cagggtgata 7800
tcacaatcac ttttcttact ttctgtccat agtacttttt catgaaagaa atttgctaaa 7860
taagacatga aaacaagact gggtagttgt agatttctgc tttttaaaat acatttgcta 7920
attttagatt atttcacaat tttaaggagc aaaatagggt cactgattcat atccaaatta 7980
tgctttgcaa ttggaaaagg gtttaaaatt ttatttatat ttctggtagt acctgtacta 8040
actgaattga aggtagtgtc tatgttattt ttgttctttt tttctgactt cgggttatgt 8100
tttcatttct ttggagtaat gctgctctag attgttctaa atagaatgtg ggcttcataa 8160
tttttttttc caaaaaaca gagtagtcaa cttatatagt caattacatc aggacatttt 8220
gtgtttctta cagaagcaaa ccataggctc ctcttttctt taaaactact tagataaact 8280
gtattcgtga actgcatgct ggaaaatgct actattatgc taaataatgc taaccaacat 8340
ttaaaatgtg caaaactaat aaagattaca ttttttattt t 8381

```

<210> 4
 <211> 2009
 <212> PRT
 <213> Homo sapiens

<400> 4
 Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe
 1 5 10 15
 Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu
 20 25 30

Lys	Ala	Lys	Asn	Pro	Lys	Pro	Asp	Lys	Lys	Asp	Asp	Asp	Glu	Asn	Gly		
		35					40				45						
Pro	Lys	Pro	Asn	Ser	Asp	Leu	Glu	Ala	Gly	Lys	Asn	Leu	Pro	Phe	Ile		
	50					55					60						
Tyr	Gly	Asp	Ile	Pro	Pro	Glu	Met	Val	Ser	Glu	Pro	Leu	Glu	Asp	Leu		
65					70					75					80		
Asp	Pro	Tyr	Tyr	Ile	Asn	Lys	Lys	Thr	Phe	Ile	Val	Leu	Asn	Lys	Leu		
				85					90					95			
Lys	Ala	Ile	Phe	Arg	Phe	Ser	Ala	Thr	Ser	Ala	Leu	Tyr	Ile	Leu	Thr		
			100					105					110				
Pro	Phe	Asn	Pro	Leu	Arg	Lys	Ile	Ala	Ile	Lys	Ile	Leu	Val	His	Ser		
		115					120					125					
Leu	Phe	Ser	Met	Leu	Ile	Met	Cys	Thr	Ile	Leu	Thr	Asn	Cys	Val	Phe		
	130					135					140						
Met	Thr	Met	Ser	Asn	Pro	Pro	Asp	Trp	Thr	Lys	Asn	Val	Glu	Tyr	Thr		
145					150					155					160		
Phe	Thr	Gly	Ile	Tyr	Thr	Phe	Glu	Ser	Leu	Ile	Lys	Ile	Ile	Ala	Arg		
			165					170						175			
Gly	Phe	Cys	Leu	Glu	Asp	Phe	Thr	Phe	Leu	Arg	Asp	Pro	Trp	Asn	Trp		
			180					185					190				
Leu	Asp	Phe	Thr	Val	Ile	Thr	Phe	Ala	Tyr	Val	Thr	Glu	Phe	Val	Asp		
	195						200				205						
Leu	Gly	Asn	Val	Ser	Ala	Leu	Arg	Thr	Phe	Arg	Val	Leu	Arg	Ala	Leu		
	210					215					220						
Lys	Thr	Ile	Ser	Val	Ile	Pro	Gly	Leu	Lys	Thr	Ile	Val	Gly	Ala	Leu		
225					230					235					240		
Ile	Gln	Ser	Val	Lys	Lys	Leu	Ser	Asp	Val	Met	Ile	Leu	Thr	Val	Phe		
			245					250						255			
Cys	Leu	Ser	Val	Phe	Ala	Leu	Ile	Gly	Leu	Gln	Leu	Phe	Met	Gly	Asn		
			260					265				270					
Leu	Arg	Asn	Lys	Cys	Ile	Gln	Trp	Pro	Pro	Thr	Asn	Ala	Ser	Leu	Glu		
		275					280				285						
Glu	His	Ser	Ile	Glu	Lys	Asn	Ile	Thr	Val	Asn	Tyr	Asn	Gly	Thr	Leu		
	290					295					300						
Ile	Asn	Glu	Thr	Val	Phe	Glu	Phe	Asp	Trp	Lys	Ser	Tyr	Ile	Gln	Asp		
305					310					315					320		
Ser	Arg	Tyr	His	Tyr	Phe	Leu	Glu	Gly	Phe	Leu	Asp	Ala	Leu	Leu	Cys		
			325					330					335				
Gly	Asn	Ser	Ser	Asp	Ala	Gly	Gln	Cys	Pro	Glu	Gly	Tyr	Met	Cys	Val		
			340					345					350				
Lys	Ala	Gly	Arg	Asn	Pro	Asn	Tyr	Gly	Tyr	Thr	Ser	Phe	Asp	Thr	Phe		
		355					360					365					
Ser	Trp	Ala	Phe	Leu	Ser	Leu	Phe	Arg	Leu	Met	Thr	Gln	Asp	Phe	Trp		
	370					375					380						
Glu	Asn	Leu	Tyr	Gln	Leu	Thr	Leu	Arg	Ala	Ala	Gly	Lys	Thr	Tyr	Met		
385					390					395					400		
Ile	Phe	Phe	Val	Leu	Val	Ile	Phe	Leu	Gly	Ser	Phe	Tyr	Leu	Ile	Asn		
			405						410					415			
Leu	Ile	Leu	Ala	Val	Val	Ala	Met	Ala	Tyr	Glu	Glu	Gln	Asn	Gln	Ala		
			420				425						430				
Thr	Leu	Glu	Glu	Ala	Glu	Gln	Lys	Glu	Ala	Glu	Phe	Gln	Gln	Met	Ile		
	435						440					445					
Glu	Gln	Leu	Lys	Lys	Gln	Gln	Glu	Ala	Ala	Gln	Gln	Ala	Ala	Thr	Ala		
	450					455					460						
Thr	Ala	Ser	Glu	His	Ser	Arg	Glu	Pro	Ser	Ala	Ala	Gly	Arg	Leu	Ser		
465					470					475					480		
Asp	Ser	Ser	Ser	Glu	Ala	Ser	Lys	Leu	Ser	Ser	Lys	Ser	Ala	Lys	Glu		
				485					490					495			

Arg	Arg	Asn	Arg	Arg	Lys	Lys	Arg	Lys	Gln	Lys	Glu	Gln	Ser	Gly	Gly		
			500					505					510				
Glu	Glu	Lys	Asp	Glu	Asp	Glu	Phe	Gln	Lys	Ser	Glu	Ser	Glu	Asp	Ser		
		515					520					525					
Ile	Arg	Arg	Lys	Gly	Phe	Arg	Phe	Ser	Ile	Glu	Gly	Asn	Arg	Leu	Thr		
	530					535					540						
Tyr	Glu	Lys	Arg	Tyr	Ser	Ser	Pro	His	Gln	Ser	Leu	Leu	Ser	Ile	Arg		
545					550					555					560		
Gly	Ser	Leu	Phe	Ser	Pro	Arg	Arg	Asn	Ser	Arg	Thr	Ser	Leu	Phe	Ser		
			565					570						575			
Phe	Arg	Gly	Arg	Ala	Lys	Asp	Val	Gly	Ser	Glu	Asn	Asp	Phe	Ala	Asp		
			580					585					590				
Asp	Glu	His	Ser	Thr	Phe	Glu	Asp	Asn	Glu	Ser	Arg	Arg	Asp	Ser	Leu		
		595					600					605					
Phe	Val	Pro	Arg	Arg	His	Gly	Glu	Arg	Arg	Asn	Ser	Asn	Leu	Ser	Gln		
	610					615					620						
Thr	Ser	Arg	Ser	Ser	Arg	Met	Leu	Ala	Val	Phe	Pro	Ala	Asn	Gly	Lys		
625					630					635					640		
Met	His	Ser	Thr	Val	Asp	Cys	Asn	Gly	Val	Val	Ser	Leu	Val	Gly	Gly		
				645				650						655			
Pro	Ser	Val	Pro	Thr	Ser	Pro	Val	Gly	Gln	Leu	Leu	Pro	Glu	Val	Ile		
			660					665					670				
Ile	Asp	Lys	Pro	Ala	Thr	Asp	Asp	Asn	Gly	Thr	Thr	Thr	Glu	Thr	Glu		
	675					680						685					
Met	Arg	Lys	Arg	Arg	Ser	Ser	Ser	Phe	His	Val	Ser	Met	Asp	Phe	Leu		
	690				695						700						
Glu	Asp	Pro	Ser	Gln	Arg	Gln	Arg	Ala	Met	Ser	Ile	Ala	Ser	Ile	Leu		
705				710					715					720			
Thr	Asn	Thr	Val	Glu	Glu	Leu	Glu	Glu	Ser	Arg	Gln	Lys	Cys	Pro	Pro		
			725					730					735				
Cys	Trp	Tyr	Lys	Phe	Ser	Asn	Ile	Phe	Leu	Ile	Trp	Asp	Cys	Ser	Pro		
		740						745					750				
Tyr	Trp	Leu	Lys	Val	Lys	His	Val	Val	Asn	Leu	Val	Val	Met	Asp	Pro		
	755					760						765					
Phe	Val	Asp	Leu	Ala	Ile	Thr	Ile	Cys	Ile	Val	Leu	Asn	Thr	Leu	Phe		
	770					775					780						
Met	Ala	Met	Glu	His	Tyr	Pro	Met	Thr	Asp	His	Phe	Asn	Asn	Val	Leu		
785				790					795						800		
Thr	Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Phe		
			805					810					815				
Leu	Lys	Ile	Ile	Ala	Met	Asp	Pro	Tyr	Tyr	Tyr	Phe	Gln	Glu	Gly	Trp		
		820						825					830				
Asn	Ile	Phe	Asp	Gly	Phe	Ile	Val	Thr	Leu	Ser	Leu	Val	Glu	Leu	Gly		
	835					840						845					
Leu	Ala	Asn	Val	Glu	Gly	Leu	Ser	Val	Leu	Arg	Ser	Phe	Arg	Leu	Leu		
	850					855					860						
Arg	Val	Phe	Lys	Leu	Ala	Lys	Ser	Trp	Pro	Thr	Leu	Asn	Met	Leu	Ile		
865				870					875					880			
Lys	Ile	Ile	Gly	Asn	Ser	Val	Gly	Ala	Leu	Gly	Asn	Leu	Thr	Leu	Val		
			885					890					895				
Leu	Ala	Ile	Ile	Val	Phe	Ile	Phe	Ala	Val	Val	Gly	Met	Gln	Leu	Phe		
		900						905					910				
Gly	Lys	Ser	Tyr	Lys	Asp	Cys	Val	Cys	Lys	Ile	Ala	Ser	Asp	Cys	Gln		
	915					920						925					
Leu	Pro	Arg	Trp	His	Met	Asn	Asp	Phe	Phe	His	Ser	Phe	Leu	Ile	Val		
	930					935					940						
Phe	Arg	Val	Leu	Cys	Gly	Glu	Trp	Ile	Glu	Thr	Met	Trp	Asp	Cys	Met		
945				950					955					960			

Glu	Val	Ala	Gly	Gln	Ala	Met	Cys	Leu	Thr	Val	Phe	Met	Met	Val	Met
				965						970				975	
Val	Ile	Gly	Asn	Leu	Val	Val	Leu	Asn	Leu	Phe	Leu	Ala	Leu	Leu	Leu
			980					985					990		
Ser	Ser	Phe	Ser	Ala	Asp	Asn	Leu	Ala	Ala	Thr	Asp	Asp	Asp	Asn	Glu
		995					1000					1005			
Met	Asn	Asn	Leu	Gln	Ile	Ala	Val	Asp	Arg	Met	His	Lys	Gly	Val	
	1010					1015					1020				
Ala	Tyr	Val	Lys	Arg	Lys	Ile	Tyr	Glu	Phe	Ile	Gln	Gln	Ser	Phe	
	1025					1030					1035				
Ile	Arg	Lys	Gln	Lys	Ile	Leu	Asp	Glu	Ile	Lys	Pro	Leu	Asp	Asp	
	1040					1045					1050				
Leu	Asn	Asn	Lys	Lys	Asp	Ser	Cys	Met	Ser	Asn	His	Thr	Thr	Glu	
	1055					1060					1065				
Ile	Gly	Lys	Asp	Leu	Asp	Tyr	Leu	Lys	Asp	Val	Asn	Gly	Thr	Thr	
	1070					1075					1080				
Ser	Gly	Ile	Gly	Thr	Gly	Ser	Ser	Val	Glu	Lys	Tyr	Ile	Ile	Asp	
	1085					1090					1095				
Glu	Ser	Asp	Tyr	Met	Ser	Phe	Ile	Asn	Asn	Pro	Ser	Leu	Thr	Val	
	1100					1105					1110				
Thr	Val	Pro	Ile	Ala	Val	Gly	Glu	Ser	Asp	Phe	Glu	Asn	Leu	Asn	
	1115					1120					1125				
Thr	Glu	Asp	Phe	Ser	Ser	Glu	Ser	Asp	Leu	Glu	Glu	Ser	Lys	Glu	
	1130					1135					1140				
Lys	Leu	Asn	Glu	Ser	Ser	Ser	Ser	Ser	Glu	Gly	Ser	Thr	Val	Asp	
	1145					1150					1155				
Ile	Gly	Ala	Pro	Val	Glu	Glu	Gln	Pro	Val	Val	Glu	Pro	Glu	Glu	
	1160					1165					1170				
Thr	Leu	Glu	Pro	Glu	Ala	Cys	Phe	Thr	Glu	Gly	Cys	Val	Gln	Arg	
	1175					1180					1185				
Phe	Lys	Cys	Cys	Gln	Ile	Asn	Val	Glu	Glu	Gly	Arg	Gly	Lys	Gln	
	1190					1195					1200				
Trp	Trp	Asn	Leu	Arg	Arg	Thr	Cys	Phe	Arg	Ile	Val	Glu	His	Asn	
	1205					1210					1215				
Trp	Phe	Glu	Thr	Phe	Ile	Val	Phe	Met	Ile	Leu	Leu	Ser	Ser	Gly	
	1220					1225					1230				
Ala	Leu	Ala	Phe	Glu	Asp	Ile	Tyr	Ile	Asp	Gln	Arg	Lys	Thr	Ile	
	1235					1240					1245				
Lys	Thr	Met	Leu	Glu	Tyr	Ala	Asp	Lys	Val	Phe	Thr	Tyr	Ile	Phe	
	1250					1255					1260				
Ile	Leu	Glu	Met	Leu	Leu	Lys	Trp	Val	Ala	Tyr	Gly	Tyr	Gln	Thr	
	1265					1270					1275				
Tyr	Phe	Thr	Asn	Ala	Trp	Cys	Trp	Leu	Asp	Phe	Leu	Ile	Val	Asp	
	1280					1285					1290				
Val	Ser	Leu	Val	Ser	Leu	Thr	Ala	Asn	Ala	Leu	Gly	Tyr	Ser	Glu	
	1295					1300					1305				
Leu	Gly	Ala	Ile	Lys	Ser	Leu	Arg	Thr	Leu	Arg	Ala	Leu	Arg	Pro	
	1310					1315					1320				
Leu	Arg	Ala	Leu	Ser	Arg	Phe	Glu	Gly	Met	Arg	Val	Val	Val	Asn	
	1325					1330					1335				
Ala	Leu	Leu	Gly	Ala	Ile	Pro	Ser	Ile	Met	Asn	Val	Leu	Leu	Leu	
	1340					1345					1350				
Cys	Leu	Ile	Phe	Trp	Leu	Ile	Phe	Ser	Ile	Met	Gly	Val	Asn	Leu	
	1355					1360					1365				
Phe	Ala	Gly	Lys	Phe	Tyr	His	Cys	Ile	Asn	Thr	Thr	Thr	Gly	Asp	
	1370					1375					1380				
Arg	Phe	Asp	Ile	Glu	Asp	Val	Asn	Asn	His	Thr	Asp	Cys	Leu	Lys	
	1385					1390					1395				

Leu	Ile	Glu	Arg	Asn	Glu	Thr	Ala	Arg	Trp	Lys	Asn	Val	Lys	Val
1400						1405					1410			
Asn	Phe	Asp	Asn	Val	Gly	Phe	Gly	Tyr	Leu	Ser	Leu	Leu	Gln	Val
1415						1420					1425			
Ala	Thr	Phe	Lys	Gly	Trp	Met	Asp	Ile	Met	Tyr	Ala	Ala	Val	Asp
1430						1435					1440			
Ser	Arg	Asn	Val	Glu	Leu	Gln	Pro	Lys	Tyr	Glu	Lys	Ser	Leu	Tyr
1445						1450					1455			
Met	Tyr	Leu	Tyr	Phe	Val	Ile	Phe	Ile	Ile	Phe	Gly	Ser	Phe	Phe
1460						1465					1470			
Thr	Leu	Asn	Leu	Phe	Ile	Gly	Val	Ile	Ile	Asp	Asn	Phe	Asn	Gln
1475						1480					1485			
Gln	Lys	Lys	Lys	Phe	Gly	Gly	Gln	Asp	Ile	Phe	Met	Thr	Glu	Glu
1490						1495					1500			
Gln	Lys	Lys	Tyr	Tyr	Asn	Ala	Met	Lys	Lys	Leu	Gly	Ser	Lys	Lys
1505						1510					1515			
Pro	Gln	Lys	Pro	Ile	Pro	Arg	Pro	Gly	Asn	Lys	Phe	Gln	Gly	Met
1520						1525					1530			
Val	Phe	Asp	Phe	Val	Thr	Arg	Gln	Val	Phe	Asp	Ile	Ser	Ile	Met
1535						1540					1545			
Ile	Leu	Ile	Cys	Leu	Asn	Met	Val	Thr	Met	Met	Val	Glu	Thr	Asp
1550						1555					1560			
Asp	Gln	Ser	Glu	Tyr	Val	Thr	Thr	Ile	Leu	Ser	Arg	Ile	Asn	Leu
1565						1570					1575			
Val	Phe	Ile	Val	Leu	Phe	Thr	Gly	Glu	Cys	Val	Leu	Lys	Leu	Ile
1580						1585					1590			
Ser	Leu	Arg	His	Tyr	Tyr	Phe	Thr	Ile	Gly	Trp	Asn	Ile	Phe	Asp
1595						1600					1605			
Phe	Val	Val	Val	Ile	Leu	Ser	Ile	Val	Gly	Met	Phe	Leu	Ala	Glu
1610						1615					1620			
Leu	Ile	Glu	Lys	Tyr	Phe	Val	Ser	Pro	Thr	Leu	Phe	Arg	Val	Ile
1625						1630					1635			
Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Lys	Gly	Ala
1640						1645					1650			
Lys	Gly	Ile	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser	Leu	Pro
1655						1660					1665			
Ala	Leu	Phe	Asn	Ile	Gly	Leu	Leu	Leu	Phe	Leu	Val	Met	Phe	Ile
1670						1675					1680			
Tyr	Ala	Ile	Phe	Gly	Met	Ser	Asn	Phe	Ala	Tyr	Val	Lys	Arg	Glu
1685						1690					1695			
Val	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Glu	Thr	Phe	Gly	Asn	Ser
1700						1705					1710			
Met	Ile	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp	Asp	Gly
1715						1720					1725			
Leu	Leu	Ala	Pro	Ile	Leu	Asn	Ser	Lys	Pro	Pro	Asp	Cys	Asp	Pro
1730						1735					1740			
Asn	Lys	Val	Asn	Pro	Gly	Ser	Ser	Val	Lys	Gly	Asp	Cys	Gly	Asn
1745						1750					1755			
Pro	Ser	Val	Gly	Ile	Phe	Phe	Phe	Val	Ser	Tyr	Ile	Ile	Ile	Ser
1760						1765					1770			
Phe	Leu	Val	Val	Val	Asn	Met	Tyr	Ile	Ala	Val	Ile	Leu	Glu	Asn
1775						1780					1785			
Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Ala	Glu	Pro	Leu	Ser	Glu	Asp
1790						1795					1800			
Asp	Phe	Glu	Met	Phe	Tyr	Glu	Val	Trp	Glu	Lys	Phe	Asp	Pro	Asp
1805						1810					1815			
Ala	Thr	Gln	Phe	Met	Glu	Phe	Glu	Lys	Leu	Ser	Gln	Phe	Ala	Ala
1820						1825					1830			

Ala	Leu	Glu	Pro	Pro	Leu	Asn	Leu	Pro	Gln	Pro	Asn	Lys	Leu	Gln
1835						1840					1845			
Leu	Ile	Ala	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile	His
1850						1855					1860			
Cys	Leu	Asp	Ile	Leu	Phe	Ala	Phe	Thr	Lys	Arg	Val	Leu	Gly	Glu
1865						1870					1875			
Ser	Gly	Glu	Met	Asp	Ala	Leu	Arg	Ile	Gln	Met	Glu	Glu	Arg	Phe
1880						1885					1890			
Met	Ala	Ser	Asn	Pro	Ser	Lys	Val	Ser	Tyr	Gln	Pro	Ile	Thr	Thr
1895						1900					1905			
Thr	Leu	Lys	Arg	Lys	Gln	Glu	Glu	Val	Ser	Ala	Val	Ile	Ile	Gln
1910						1915					1920			
Arg	Ala	Tyr	Arg	Arg	His	Leu	Leu	Lys	Arg	Thr	Val	Lys	Gln	Ala
1925						1930					1935			
Ser	Phe	Thr	Tyr	Asn	Lys	Asn	Lys	Ile	Lys	Gly	Gly	Ala	Asn	Leu
1940						1945					1950			
Leu	Ile	Lys	Glu	Asp	Met	Ile	Ile	Asp	Arg	Ile	Asn	Glu	Asn	Ser
1955						1960					1965			
Ile	Thr	Glu	Lys	Thr	Asp	Leu	Thr	Met	Ser	Thr	Ala	Ala	Cys	Pro
1970						1975					1980			
Pro	Ser	Tyr	Asp	Arg	Val	Thr	Lys	Pro	Ile	Val	Glu	Lys	His	Glu
1985						1990					1995			
Gln	Glu	Gly	Lys	Asp	Glu	Lys	Ala	Lys	Gly	Lys				
2000						2005								

<210> 5
 <211> 8381
 <212> DNA
 <213> Homo sapiens

<400> 5
 atactgcaga ggtctctggt gcatgtgtgt atgtgtgcgt ttgtgtgtgt ttgtgtgtct 60
 gtgtgttctg cccagtgag actgcagccc ttgtaaatac ttgacacct tttgcaagaa 120
 ggaatctgaa caattgcaac tgaaggcaca ttgttatcat ctctcttttg ggtgatgctg 180
 ttcctcactg cagatggata attttccttt taatcaggaa tttcatatgc agaataaatg 240
 gtaattaaaa tgtgcaggat gacaagatgg agcaaacagt gcttgtacca ccaggacctg 300
 acagcttcaa cttcttcacc agagaatctc ttgctggctat tgaaagacgc attgcagaag 360
 aaaaggcaaa gaatcccaa ccagacaaaa aagatgacga cgaaaatggc ccaaagccaa 420
 atagtgactt ggaagctgga aagaaccttc catttattta tggagacatt cctccagaga 480
 tgggtgtcaga gccctggag gacctggacc cctactatat caataagaaa acttttatag 540
 tattgaataa attgaaggcc atcttccggt tcagtgccac ctctgccctg tacattttta 600
 ctcccttcaa tcctcttagg aaaatagcta ttaagatttt ggtacattca ttattcagca 660
 tgctaattat gtgcactatt ttgacaaact gtgtgtttat gacaatgagt aaccctcctg 720
 attggacaaa gaatgtagaa tacaccttca caggaatata tacttttgaa tcacttataa 780
 aaattattgc aaggggattc tgtttagaag attttacttt ccttcgggat ccatggaact 840
 ggctcgattt cactgtcatt acatttgcgt acgtcacaga gtttgtggac ctgggcaatg 900
 tctcggcatt gagaacattc agagtctctc gagcattgaa gacgatttca gtcattccag 960
 gcctgaaaac cattgtggga gccctgatcc agtctgtgaa gaagctctca gatgtaatga 1020
 tcctgactgt gttctgtctg agcgtatttg ctctaattgg gctgcagctg ttcattgggca 1080
 acctgaggaa taaatgtata caatggcctc ccaccaatgc ttccttggag gaacatagta 1140
 tagaaaagaa tataactgtg aattataatg gtacacttat aaatgaaact gtctttgagt 1200
 ttgactggaa gtcatatatt caagattcaa gatatcatta tttcctggag ggttttttag 1260
 atgcactact atgtggaaat agctctgatg caggccaatg tccagaggga tatatgtgtg 1320
 tgaaagctgg tagaaatccc aattatggct acacaagctt tgataccttc agttgggctt 1380
 ttttgtcctt gtttcgacta atgactcagg acttctggga aaatctttat caactgacat 1440
 tacgtgctgc tgggaaaacg tacatgatat tttttgtatt ggtcattttc ttgggctcat 1500
 tctacctaat aaatttgatc ctggctgtgg tggccatggc ctacgaggaa cagaatcagg 1560
 ccaccttgga agaagcagaa cagaaagagg ccgaatttca gcagatgatt gaacagctta 1620

aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcctcagaa	cattccagag	1680
agcccagtgc	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgctaa	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aaggttttcg	cttctccatt	gaaggggaacc	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atccgtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagctttaga	gggcgagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtggt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtggttt	2220
ccttggttgg	tggaccttca	gttcctacat	cgctgttgg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaaggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacaa	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttgg	tataaatttt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattgggt	aaaagtgaag	catgttgtca	acctgggtgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaataa	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttctct	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggtttt	attgtgacgc	ttagcctggt	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaataatg	ctaataaaga	tcacgggcaa	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcatttttgc	cgtggtcggc	atgcagctct	3000
ttggtaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtggt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcatgatggt	catggtgatt	ggaaacctag	tggctcctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgacg	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aatttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagtctta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaattttaa	acggaagact	3660
ttagtagtga	atcggatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaatatgc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tatttcacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaattctct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggg	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatattctgg	ctaattttca	gcatcatggg	cgtaaatttg	tttgctggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attgggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatgggtctt	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcaccaatg	atgggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctatttac	tggagagtgt	gtactgaaac	5040
tcattctctct	acgccattat	tattttacca	ttggatggaa	tatttttgat	tttgtgggtg	5100
tcattctctc	cattgtagggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160

ctaccctggt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatgcgcacg	ctgctctttg	ctttgatgat	gtcccttcct	gcgttggtta	5280
acateggcct	cctactcttc	ctagtcatgt	tcactctacg	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatgtt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgactgtg	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttcct	ggttgtggtg	aacatgtaca	tcgcggtcat	cctggagAAC	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgagggtt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcattggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaacccaa	caaactccag	ctcattgccA	5820
tggatttgcc	catggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaaggtct	cctatcagcc	aatcactact	actttaaaac	6000
gaaaacaaga	ggaagtatct	gctgtcatta	ttcagcgtgc	ttacagacgc	caccttttaa	6060
agcgaactgt	aaaacaagct	tcctttacgt	acaataaaaa	caaaatcaaa	ggtggggcta	6120
atcttcttat	aaaagaagac	atgataattg	acagaataaa	tgaaaactct	attacagaaa	6180
aaactgatct	gaccatgtcc	actgcagctt	gtccaccttc	ctatgaccgg	gtgacaaagc	6240
caattgtgga	aaaacatgag	caagaaggca	aagatgaaaa	agccaaaggg	aaataaatga	6300
aaataaataa	aaataattgg	gtgacaaatt	gtttacagcc	tgtgaagggtg	atgtattttt	6360
atcaacagga	ctccttttagg	aggccaatgc	caaactgact	gttttttacac	aaatctcctt	6420
aaggtcagtg	cctacaataa	gacagtgacc	ccttgtcagc	aaactgtgac	tctgtgtaaa	6480
ggggagatga	ccttgacagg	aggttactgt	tctcactacc	agctgacact	gctgaagata	6540
agatgcacaa	tggctagtca	gactgtaggg	accagtttca	aggggtgcaa	acctgtgatt	6600
ttgggggtgt	ttaacatgaa	acacttttagt	gtagtaattg	tatccactgt	ttgcatttca	6660
actgccacat	ttgtcacatt	tttatggaat	ctgttagtgg	attcatcttt	ttgttaatcc	6720
atgtgtttat	tatatgtgac	tattttttgta	aacgaagttt	ctgttgagaa	ataggctaag	6780
gacctctata	acaggatatgc	cacctggggg	gtatggcaac	cacatggccc	tcccagctac	6840
acaaagtcgt	ggtttgcatg	agggcatgct	gcacttagag	atcatgcatg	agaaaaagtc	6900
acaagaaaaa	caaattctta	aatttcacca	tattttctggg	aggggttaatt	gggtgataag	6960
tggaggtgct	ttgttgatct	tgttttgCGA	aatccagccc	ctagaccaag	tagattattt	7020
gtgggtaggc	cagtaaatct	tagcagggtgc	aaacttcatt	caaatgtttg	gagtcataaa	7080
tgttatgttt	ctttttgttg	tattaaaaaa	aaaacctgaa	tagtgaatat	tgccccctcac	7140
cctccaccgc	cagaagactg	aattgaccaa	aattactctt	tataaatttc	tgctttttcc	7200
tgcactttgt	ttagccatct	ttgggctctc	agcaagggtg	acactgtata	tgttaatgaa	7260
atgctattta	ttatgtaaat	agtcatttta	ccctgtggtg	cacgtttgag	caaacaaata	7320
atgacctaaG	cacagtattt	attgcatcaa	atatgtacca	caagaaatgt	agagtgcAag	7380
ctttacacag	gtaataaaaat	gtattctgta	ccatttatag	atagtttgga	tgctatcaat	7440
gcatgtttat	attaccatgc	tgctgtatct	ggtttctctc	actgctcaga	atctcattta	7500
tgagaaacca	tatgtcagtg	gtaaagtcaa	ggaaattgtt	caacagatct	catttattta	7560
agtcattaag	caatagtttg	cagcacttta	acagcttttt	ggttattttt	acattttaag	7620
tggataacat	atggtatata	gccagactgt	acagacatgt	ttaaaaaaac	acactgctta	7680
acctattaaa	tatgtgttta	gaattttata	agcaaataata	aatactgtaa	aaagtcactt	7740
tattttattt	ttcagcatta	tgtacataaa	tatgaagagg	aaattatctt	caggttgata	7800
tcacaatcac	ttttcttact	ttctgtccat	agtacttttt	catgaaagaa	atttgctaaa	7860
taagacatga	aaacaagact	gggtagtgtg	agatttctgc	tttttaaatt	acatttgcta	7920
attttagatt	atttcacaa	tttaaggagc	aaaatagggt	cacgattcat	atccaaatta	7980
tgctttgcaa	ttggaaaagg	gtttaaaatt	ttatttatat	ttctggtagt	acctgtacta	8040
actgaattga	aggtagtgct	tatgttattt	ttgttctttt	ttctgactt	cggtttatgt	8100
tttcattttct	ttggagtaat	gctgctctag	attgttctaa	atagaatgtg	ggcttcataa	8160
tttttttttc	cacaaaaaca	gagtagtcaa	cttatatagt	caattacatc	aggacatttt	8220
gtgtttctta	cagaagcaaa	ccataggctc	ctcttttctt	taaaactact	tagataaact	8280
gtattcgtga	actgcatgct	ggaaaatgct	actattatgc	taaataatgc	taaccaacat	8340
ttaaaatgtg	caaaactaat	aaagattaca	ttttttattt	t		8381

<210> 6
 <211> 2009
 <212> PRT
 <213> Homo sapiens

```

<400> 6
Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe
1          5          10          15
Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu
20          25          30
Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly
35          40          45
Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
50          55          60
Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
65          70          75          80
Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu
85          90          95
Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
100         105         110
Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser
115         120         125
Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
130         135         140
Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145         150         155         160
Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg
165         170         175
Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
180         185         190
Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp
195         200         205
Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
210         215         220
Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225         230         235         240
Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
245         250         255
Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
260         265         270
Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu
275         280         285
Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu
290         295         300
Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp
305         310         315         320
Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys
325         330         335
Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val
340         345         350
Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe
355         360         365
Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp
370         375         380
Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met
385         390         395         400
Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn
405         410         415
Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala
420         425         430
Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile
435         440         445
Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala
450         455         460

```

Thr	Ala	Ser	Glu	His	Ser	Arg	Glu	Pro	Ser	Ala	Ala	Gly	Arg	Leu	Ser	465	470	475	480
Asp	Ser	Ser	Ser	Glu	Ala	Ser	Lys	Leu	Ser	Ser	Lys	Ser	Ala	Lys	Glu				
				485					490						495				
Arg	Arg	Asn	Arg	Arg	Lys	Lys	Arg	Lys	Gln	Lys	Glu	Gln	Ser	Gly	Gly	500	505	510	
Glu	Glu	Lys	Asp	Glu	Asp	Glu	Phe	Gln	Lys	Ser	Glu	Ser	Glu	Asp	Ser	515	520	525	
Ile	Arg	Arg	Lys	Gly	Phe	Arg	Phe	Ser	Ile	Glu	Gly	Asn	Arg	Leu	Thr	530	535	540	
Tyr	Glu	Lys	Arg	Tyr	Ser	Ser	Pro	His	Gln	Ser	Leu	Leu	Ser	Ile	Arg	545	550	555	560
Gly	Ser	Leu	Phe	Ser	Pro	Arg	Arg	Asn	Ser	Arg	Thr	Ser	Leu	Phe	Ser		565	570	575
Phe	Arg	Gly	Arg	Ala	Lys	Asp	Val	Gly	Ser	Glu	Asn	Asp	Phe	Ala	Asp	580	585	590	
Asp	Glu	His	Ser	Thr	Phe	Glu	Asp	Asn	Glu	Ser	Arg	Arg	Asp	Ser	Leu	595	600	605	
Phe	Val	Pro	Arg	Arg	His	Gly	Glu	Arg	Arg	Asn	Ser	Asn	Leu	Ser	Gln	610	615	620	
Thr	Ser	Arg	Ser	Ser	Arg	Met	Leu	Ala	Val	Phe	Pro	Ala	Asn	Gly	Lys	625	630	635	640
Met	His	Ser	Thr	Val	Asp	Cys	Asn	Gly	Val	Val	Ser	Leu	Val	Gly	Gly		645	650	655
Pro	Ser	Val	Pro	Thr	Ser	Pro	Val	Gly	Gln	Leu	Leu	Pro	Glu	Val	Ile	660	665	670	
Ile	Asp	Lys	Pro	Ala	Thr	Asp	Asp	Asn	Gly	Thr	Thr	Thr	Glu	Thr	Glu	675	680	685	
Met	Arg	Lys	Arg	Arg	Ser	Ser	Ser	Phe	His	Val	Ser	Met	Asp	Phe	Leu	690	695	700	
Glu	Asp	Pro	Ser	Gln	Arg	Gln	Arg	Ala	Met	Ser	Ile	Ala	Ser	Ile	Leu	705	710	715	720
Thr	Asn	Thr	Val	Glu	Glu	Leu	Glu	Glu	Ser	Arg	Gln	Lys	Cys	Pro	Pro		725	730	735
Cys	Trp	Tyr	Lys	Phe	Ser	Asn	Ile	Phe	Leu	Ile	Trp	Asp	Cys	Ser	Pro	740	745	750	
Tyr	Trp	Leu	Lys	Val	Lys	His	Val	Val	Asn	Leu	Val	Val	Met	Asp	Pro	755	760	765	
Phe	Val	Asp	Leu	Ala	Ile	Thr	Ile	Cys	Ile	Val	Leu	Asn	Thr	Leu	Phe	770	775	780	
Met	Ala	Met	Glu	His	Tyr	Pro	Met	Thr	Asp	His	Phe	Asn	Asn	Val	Leu	785	790	795	800
Thr	Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Phe		805	810	815
Leu	Lys	Ile	Ile	Ala	Met	Asp	Pro	Tyr	Tyr	Tyr	Phe	Gln	Glu	Gly	Trp	820	825	830	
Asn	Ile	Phe	Asp	Gly	Phe	Ile	Val	Thr	Leu	Ser	Leu	Val	Glu	Leu	Gly	835	840	845	
Leu	Ala	Asn	Val	Glu	Gly	Leu	Ser	Val	Leu	Arg	Ser	Phe	Arg	Leu	Leu	850	855	860	
Arg	Val	Phe	Lys	Leu	Ala	Lys	Ser	Trp	Pro	Thr	Leu	Asn	Met	Leu	Ile	865	870	875	880
Lys	Ile	Ile	Gly	Asn	Ser	Val	Gly	Ala	Leu	Gly	Asn	Leu	Thr	Leu	Val		885	890	895
Leu	Ala	Ile	Ile	Val	Phe	Ile	Phe	Ala	Val	Val	Gly	Met	Gln	Leu	Phe	900	905	910	
Gly	Lys	Ser	Tyr	Lys	Asp	Cys	Val	Cys	Lys	Ile	Ala	Ser	Asp	Cys	Gln	915	920	925	

Leu	Pro	Arg	Trp	His	Met	Asn	Asp	Phe	Phe	His	Ser	Phe	Leu	Ile	Val
930						935					940				
Phe	Arg	Val	Leu	Cys	Gly	Glu	Trp	Ile	Glu	Thr	Met	Trp	Asp	Cys	Met
945					950					955					960
Glu	Val	Ala	Gly	Gln	Ala	Met	Cys	Leu	Thr	Val	Phe	Met	Met	Val	Met
				965					970					975	
Val	Ile	Gly	Asn	Leu	Val	Val	Leu	Asn	Leu	Phe	Leu	Ala	Leu	Leu	Leu
			980					985					990		
Ser	Ser	Phe	Ser	Ala	Asp	Asn	Leu	Ala	Ala	Thr	Asp	Asp	Asp	Asn	Glu
		995					1000					1005			
Met	Asn	Asn	Leu	Gln	Ile	Ala	Val	Asp	Arg	Met	His	Lys	Gly	Val	
1010						1015					1020				
Ala	Tyr	Val	Lys	Arg	Lys	Ile	Tyr	Glu	Phe	Ile	Gln	Gln	Ser	Phe	
1025						1030					1035				
Ile	Arg	Lys	Gln	Lys	Ile	Leu	Asp	Glu	Ile	Lys	Pro	Leu	Asp	Asp	
1040						1045					1050				
Leu	Asn	Asn	Lys	Lys	Asp	Ser	Cys	Met	Ser	Asn	His	Thr	Thr	Glu	
1055						1060					1065				
Ile	Gly	Lys	Asp	Leu	Asp	Tyr	Leu	Lys	Asp	Val	Asn	Gly	Thr	Thr	
1070						1075					1080				
Ser	Gly	Ile	Gly	Thr	Gly	Ser	Ser	Val	Glu	Lys	Tyr	Ile	Ile	Asp	
1085						1090					1095				
Glu	Ser	Asp	Tyr	Met	Ser	Phe	Ile	Asn	Asn	Pro	Ser	Leu	Thr	Val	
1100						1105					1110				
Thr	Val	Pro	Ile	Ala	Val	Gly	Glu	Ser	Asp	Phe	Glu	Asn	Leu	Asn	
1115						1120					1125				
Thr	Glu	Asp	Phe	Ser	Ser	Glu	Ser	Asp	Leu	Glu	Glu	Ser	Lys	Glu	
1130						1135					1140				
Lys	Leu	Asn	Glu	Ser	Ser	Ser	Ser	Ser	Glu	Gly	Ser	Thr	Val	Asp	
1145						1150					1155				
Ile	Gly	Ala	Pro	Val	Glu	Glu	Gln	Pro	Val	Val	Glu	Pro	Glu	Glu	
1160						1165					1170				
Thr	Leu	Glu	Pro	Glu	Ala	Cys	Phe	Thr	Glu	Gly	Cys	Val	Gln	Arg	
1175						1180					1185				
Phe	Lys	Cys	Cys	Gln	Ile	Asn	Val	Glu	Glu	Gly	Arg	Gly	Lys	Gln	
1190						1195					1200				
Trp	Trp	Asn	Leu	Arg	Arg	Thr	Cys	Phe	Arg	Ile	Val	Glu	His	Asn	
1205						1210					1215				
Trp	Phe	Glu	Thr	Phe	Ile	Val	Phe	Met	Ile	Leu	Leu	Ser	Ser	Gly	
1220						1225					1230				
Ala	Leu	Ala	Phe	Glu	Asp	Ile	Tyr	Ile	Asp	Gln	Arg	Lys	Thr	Ile	
1235						1240					1245				
Lys	Thr	Met	Leu	Glu	Tyr	Ala	Asp	Lys	Val	Phe	Thr	Tyr	Ile	Phe	
1250						1255					1260				
Ile	Leu	Glu	Met	Leu	Leu	Lys	Trp	Val	Ala	Tyr	Gly	Tyr	Gln	Thr	
1265						1270					1275				
Tyr	Phe	Thr	Asn	Ala	Trp	Cys	Trp	Leu	Asp	Phe	Leu	Ile	Val	Asp	
1280						1285					1290				
Val	Ser	Leu	Val	Ser	Leu	Thr	Ala	Asn	Ala	Leu	Gly	Tyr	Ser	Glu	
1295						1300					1305				
Leu	Gly	Ala	Ile	Lys	Ser	Leu	Arg	Thr	Leu	Arg	Ala	Leu	Arg	Pro	
1310						1315					1320				
Leu	Arg	Ala	Leu	Ser	Arg	Phe	Glu	Gly	Met	Arg	Val	Val	Val	Asn	
1325						1330					1335				
Ala	Leu	Leu	Gly	Ala	Ile	Pro	Ser	Ile	Met	Asn	Val	Leu	Leu	Val	
1340						1345					1350				
Cys	Leu	Ile	Phe	Trp	Leu	Ile	Phe	Ser	Ile	Met	Gly	Val	Asn	Leu	
1355						1360					1365				

Phe	Ala	Gly	Lys	Phe	Tyr	His	Cys	Ile	Asn	Thr	Thr	Thr	Gly	Asp
1370						1375						1380		
Arg	Phe	Asp	Ile	Glu	Asp	Val	Asn	Asn	His	Thr	Asp	Cys	Leu	Lys
1385						1390						1395		
Leu	Ile	Glu	Arg	Asn	Glu	Thr	Ala	Arg	Trp	Lys	Asn	Val	Lys	Val
1400						1405						1410		
Asn	Phe	Asp	Asn	Val	Gly	Phe	Gly	Tyr	Leu	Ser	Leu	Leu	Gln	Val
1415						1420						1425		
Ala	Thr	Phe	Lys	Gly	Trp	Met	Asp	Ile	Met	Tyr	Ala	Ala	Val	Asp
1430						1435						1440		
Ser	Arg	Asn	Val	Glu	Leu	Gln	Pro	Lys	Tyr	Glu	Lys	Ser	Leu	Tyr
1445						1450						1455		
Met	Tyr	Leu	Tyr	Phe	Val	Ile	Phe	Ile	Ile	Phe	Gly	Ser	Phe	Phe
1460						1465						1470		
Thr	Leu	Asn	Leu	Phe	Ile	Gly	Val	Ile	Ile	Asp	Asn	Phe	Asn	Gln
1475						1480						1485		
Gln	Lys	Lys	Lys	Phe	Gly	Gly	Gln	Asp	Ile	Phe	Met	Thr	Glu	Glu
1490						1495						1500		
Gln	Lys	Lys	Tyr	Tyr	Asn	Ala	Met	Lys	Lys	Leu	Gly	Ser	Lys	Lys
1505						1510						1515		
Pro	Gln	Lys	Pro	Ile	Pro	Arg	Pro	Gly	Asn	Lys	Phe	Gln	Gly	Met
1520						1525						1530		
Val	Phe	Asp	Phe	Val	Thr	Arg	Gln	Val	Phe	Asp	Ile	Ser	Ile	Met
1535						1540						1545		
Ile	Leu	Ile	Cys	Leu	Asn	Met	Val	Thr	Met	Met	Val	Glu	Thr	Asp
1550						1555						1560		
Asp	Gln	Ser	Glu	Tyr	Val	Thr	Thr	Ile	Leu	Ser	Arg	Ile	Asn	Leu
1565						1570						1575		
Val	Phe	Ile	Val	Leu	Phe	Thr	Gly	Glu	Cys	Val	Leu	Lys	Leu	Ile
1580						1585						1590		
Ser	Leu	Arg	His	Tyr	Tyr	Phe	Thr	Ile	Gly	Trp	Asn	Ile	Phe	Asp
1595						1600						1605		
Phe	Val	Val	Val	Ile	Leu	Ser	Ile	Val	Gly	Met	Phe	Leu	Ala	Glu
1610						1615						1620		
Leu	Ile	Glu	Lys	Tyr	Phe	Val	Ser	Pro	Thr	Leu	Phe	Arg	Val	Ile
1625						1630						1635		
Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Lys	Gly	Ala
1640						1645						1650		
Lys	Gly	Met	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser	Leu	Pro
1655						1660						1665		
Ala	Leu	Phe	Asn	Ile	Gly	Leu	Leu	Leu	Phe	Leu	Val	Met	Phe	Ile
1670						1675						1680		
Tyr	Ala	Ile	Phe	Gly	Met	Ser	Asn	Phe	Ala	Tyr	Val	Lys	Arg	Glu
1685						1690						1695		
Val	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Glu	Thr	Phe	Gly	Asn	Ser
1700						1705						1710		
Met	Ile	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp	Asp	Gly
1715						1720						1725		
Leu	Leu	Ala	Pro	Ile	Leu	Asn	Ser	Lys	Pro	Pro	Asp	Cys	Asp	Pro
1730						1735						1740		
Asn	Lys	Val	Asn	Pro	Gly	Ser	Ser	Val	Lys	Gly	Asp	Cys	Gly	Asn
1745						1750						1755		
Pro	Ser	Val	Gly	Ile	Phe	Phe	Phe	Val	Ser	Tyr	Ile	Ile	Ile	Ser
1760						1765						1770		
Phe	Leu	Val	Val	Val	Asn	Met	Tyr	Ile	Ala	Val	Ile	Leu	Glu	Asn
1775						1780						1785		
Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Ala	Glu	Pro	Leu	Ser	Glu	Asp
1790						1795						1800		

Asp	Phe	Glu	Met	Phe	Tyr	Glu	Val	Trp	Glu	Lys	Phe	Asp	Pro	Asp	
1805						1810					1815				
Ala	Thr	Gln	Phe	Met	Glu	Phe	Glu	Lys	Leu	Ser	Gln	Phe	Ala	Ala	
1820						1825					1830				
Ala	Leu	Glu	Pro	Pro	Leu	Asn	Leu	Pro	Gln	Pro	Asn	Lys	Leu	Gln	
1835						1840					1845				
Leu	Ile	Ala	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile	His	
1850						1855					1860				
Cys	Leu	Asp	Ile	Leu	Phe	Ala	Phe	Thr	Lys	Arg	Val	Leu	Gly	Glu	
1865						1870					1875				
Ser	Gly	Glu	Met	Asp	Ala	Leu	Arg	Ile	Gln	Met	Glu	Glu	Arg	Phe	
1880						1885					1890				
Met	Ala	Ser	Asn	Pro	Ser	Lys	Val	Ser	Tyr	Gln	Pro	Ile	Thr	Thr	
1895						1900					1905				
Thr	Leu	Lys	Arg	Lys	Gln	Glu	Glu	Val	Ser	Ala	Val	Ile	Ile	Gln	
1910						1915					1920				
Arg	Ala	Tyr	Arg	Arg	His	Leu	Leu	Lys	Arg	Thr	Val	Lys	Gln	Ala	
1925						1930					1935				
Ser	Phe	Thr	Tyr	Asn	Lys	Asn	Lys	Ile	Lys	Gly	Gly	Ala	Asn	Leu	
1940						1945					1950				
Leu	Ile	Lys	Glu	Asp	Met	Ile	Ile	Asp	Arg	Ile	Asn	Glu	Asn	Ser	
1955						1960					1965				
Ile	Thr	Glu	Lys	Thr	Asp	Leu	Thr	Met	Ser	Thr	Ala	Ala	Cys	Pro	
1970						1975					1980				
Pro	Ser	Tyr	Asp	Arg	Val	Thr	Lys	Pro	Ile	Val	Glu	Lys	His	Glu	
1985						1990					1995				
Gln	Glu	Gly	Lys	Asp	Glu	Lys	Ala	Lys	Gly	Lys					
2000						2005									

<210> 7
 <211> 8381
 <212> DNA
 <213> Homo sapiens

<400> 7

atactgcaga	ggctctctggt	gcatgtgtgt	atgtgtgcgt	ttgtgtgtgt	ttgtgtgtct	60
gtgtgttctg	ccccagtgag	actgcagccc	ttgtaaatac	tttgacacct	tttgcaagaa	120
ggaatctgaa	caattgcaac	tgaaggcaca	ttgttatcat	ctcgtctttg	ggatgatgctg	180
ttcctcactg	cagatggata	attttccttt	taatcaggaa	tttcatatgc	agaataaatg	240
gtaattaaaa	tgtgcaggat	gacaagatgg	agcaaacagt	gcttgtacca	ccaggacctg	300
acagcttcaa	cttcttcacc	agagaatctc	ttgcggctat	tgaaagacgc	attgcagaag	360
aaaaggcaaa	gaatcccaaa	ccagacaaaa	aagatgacga	cgaaaatggc	ccaaagccaa	420
atagtgactt	ggaagctgga	aagaaccttc	catttattta	tggagacatt	cctccagaga	480
tggtgtcaga	gcccctggag	gacctggacc	cctactatat	caataagaaa	acttttatag	540
tattgaataa	attgaaggcc	atcttcoggt	tcagtgccac	ctctgccctg	tacattttaa	600
ctcccttcaa	tcctcttagg	aaaatagcta	ttaagatttt	ggtacattca	ttattcagca	660
tgctaattat	gtgcactatt	ttgacaaact	gtgtgtttat	gacaatgagt	aaccctcctg	720
attggacaaa	gaatgtagaa	tacaccttca	caggaatata	tacttttgaa	tcacttataa	780
aaattattgc	aaggggattc	tgtttagaag	attttacttt	ccttcgggat	ccatggaact	840
ggctcgattt	cactgtcatt	acatttgcgt	acgtcacaga	gtttgtggac	ctgggcaatg	900
tctcggcatt	gagaacattc	agagttctcc	gagcattgaa	gacgatttca	gtcattccag	960
gcctgaaaac	cattgtggga	gccctgatcc	agtctgtgaa	gaagctctca	gatgtaatga	1020
tcctgactgt	gttctgtctg	agcgtatttg	ctctaattgg	gctgcagctg	ttcatgggca	1080
acctgaggaa	taaatgtata	caatggcctc	ccaccaatgc	ttccttggag	gaacatagta	1140
tagaaaagaa	tataactgtg	aattataatg	gtacacttat	aaatgaaact	gtctttgagt	1200
ttgactggaa	gtcatatatt	caagattcaa	gatataatta	tttcctggag	ggtttttttag	1260
atgcactact	atgtggaaat	agctctgatg	caggccaatg	tccagaggga	tatatgtgtg	1320
tgaaagctgg	tagaaatccc	aattatggct	acacaagctt	tgataccttc	agttgggctt	1380
ttttgtcctt	gtttcgacta	atgactcagg	acttctggga	aaatctttat	caactgacat	1440

tacgtgctgc	tgggaaaacg	tacatgatat	tttttgtatt	ggtcattttc	ttgggctcat	1500
tctaccta	aaatttgate	ctggctgtgg	tggccatggc	ctacgaggaa	cagaatcagg	1560
ccaccttga	agaagcagaa	cagaaagagg	ccgaatttca	gcagatgatt	gaacagctta	1620
aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcctcagaa	cattccagag	1680
agcccagtg	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgttaa	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctgggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aaggttttcg	cttctccatt	gaagggaaac	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atccgtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagctttaga	gggagagcaa	aggatgtggg	atctgagaa	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtggt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtgggtt	2220
ccttggttgg	tggaccttca	gttcctacat	cgcctgttgg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaagggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacaa	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttgg	tataaatttt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattgggt	aaaagtga	catgttgtca	acctggttgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaaata	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttca	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggttt	attgtgaggc	ttagcctggt	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaataatg	ctaataaaga	tcatcgga	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcatttttgc	cgtggtcggc	atgcagctct	3000
ttggtaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtgtt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcatgatgg	catggtgatt	ggaaacctag	tggctctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgcag	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aatttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagcttta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaattttaa	acggaagact	3660
ttagtagtga	atcggatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaaatagc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tatttcacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaactctc	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggt	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatattctgg	ctaattttca	gcatcatggg	cgtaaatttg	tttgcaggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attgggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatggtctt	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atgggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctattttac	tggagagtgt	gtactgaaac	5040

tcattctctct	acgccattat	tatttttacca	ttggatggaa	tattttttgat	tttgtggttg	5100
tcattctctc	cattgtaggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160
ctaccctgtt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttcct	gcgttgttta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcattctacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatgtt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgactgtg	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttcct	ggttgtggtg	aacatgtaca	tcgcggtcat	cctggagaac	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgaggttt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcattggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaaccaaa	caaactccag	ctcattgccca	5820
tggatttgcc	catggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaagggtc	cctatcagcc	aatcactact	actttaaaac	6000
gaaaacaaga	ggaagtatct	gctgtcatta	ttcagcgtgc	ttacagacgc	caccttttaa	6060
agcgaactgt	aaaacaagct	tccttttacgt	acaataaaaa	caaaatcaaa	ggtggggcta	6120
atcttcttat	aaaagaagac	atgataattg	acagaataaa	tgaaaactct	attacagaaa	6180
aaactgatct	gaccatgtcc	actgcagctt	gtccaccttc	ctatgaccgg	gtgacaaagc	6240
caattgtgga	aaaacatgag	caagaaggca	aagatgaaaa	agccaaaggg	aaataaatga	6300
aaataaataa	aaataattgg	gtgacaaatt	gtttacagcc	tgtgaagggtg	atgtattttt	6360
atcaacagga	ctcctttagg	aggtaaatgc	caaactgact	gtttttacac	aaatctcctt	6420
aaggtcagt	cctacaataa	gacagtgacc	ccttgtcagc	aaactgtgac	tctgtgtaaa	6480
ggggagatga	ccttgacagg	aggttactgt	tctcactacc	agctgacact	gctgaagata	6540
agatgcacaa	tggctagtca	gactgtaggg	accagtttca	aggggtgcaa	acctgtgatt	6600
ttgggggttg	ttaacatgaa	acactttagt	gtagtaattg	tatccactgt	ttgcatttca	6660
actgccacat	ttgtcacatt	tttatggaat	ctgttagtg	attcatcttt	ttgttaatcc	6720
atgtgtttat	tatatgtgac	tattttttgta	aacgaagttt	ctgttgagaa	ataggctaag	6780
gacctctata	acaggtatgc	cacctggggg	gtatggcaac	cacatggccc	tcccagctac	6840
acaaagtcgt	ggtttgcatg	agggcatgct	gcacttagag	atcatgcatg	agaaaaagtc	6900
acaagaaaaa	caaattctta	aatttcacca	tattttctggg	aggggttaatt	gggtgataag	6960
tggaggtgct	ttgttgatct	tgttttgcca	aatccagccc	ctagaccaag	tagattattt	7020
gtgggtaggg	cagtaaatct	tagcaggtgc	aaacttcatt	caaagtgttg	gagtcataaa	7080
tgttatgttt	ctttttgttg	tattaaaaaa	aaaacctgaa	tagtgaatat	tgccccctcac	7140
cctccaccgc	cagaagactg	aattgaccaa	aattactctt	tataaatttc	tgctttttcc	7200
tgcactttgt	ttagccatct	ttgggctctc	agcaagggtg	acactgtata	tgttaatgaa	7260
atgctattta	ttatgtaaat	agtcatttta	ccctgtgggtg	cacgtttgag	caaacaaata	7320
atgacctaag	cacagtattt	attgcatcaa	atatgtacca	caagaaatgt	agagtgcag	7380
ctttacacag	gtaataaaat	gtattctgta	ccattttatag	atagtttgga	tgctatcaat	7440
gcatgtttat	attaccatgc	tgctgtatct	ggtttctctc	actgctcaga	atctcattta	7500
tgagaaacca	tatgtcagtg	gtaaaagtcaa	ggaaattgtt	caacagatct	cattttattta	7560
agtcattaag	caatagtttg	cagcacttta	acagcttttt	ggttattttt	acatttttaag	7620
tggataacat	atggtatata	gccagactgt	acagacatgt	ttaaaaaaac	acactgctta	7680
acctattaaa	tatgtgttta	gaattttata	agcaaataata	aatactgtaa	aaagtcactt	7740
tatttttattt	ttcagcatta	tgtacataaa	tatgaagagg	aaattatctt	caggttgata	7800
tcacaatcac	ttttcttact	ttctgtccat	agtacttttt	catgaaagaa	atttgctaaa	7860
taagacatga	aaacaagact	gggtagtgtg	agattttctgc	tttttaaaatt	acatttgcta	7920
attttagatt	atttcacaa	tttaaggagc	aaaatagggtt	cacgattcat	atccaaatta	7980
tgctttgcaa	ttggaaaagg	gtttaaaatt	ttattttatat	ttctggtagt	acctgtacta	8040
actgaattga	aggtagtgct	tatgttattt	ttgttctttt	tttctgactt	cggtttatgt	8100
tttcatttct	ttggagtaat	gctgctctag	attgttctaa	atagaatgtg	ggcttcataa	8160
tttttttttt	cacaaaaaca	gagtagtcaa	cttatatagt	caattacatc	aggacatttt	8220
gtgtttctta	cagaagcaaa	ccataggctc	ctcttttctt	taaaactact	tagataaaact	8280
gtattcgtga	actgcatgct	ggaaaatgct	actattatgc	taaataatgc	taaccaacat	8340
ttaaaatgtg	caaaactaat	aaagattaca	tttttttattt	t		8381

<210> 8

<211> 8381

<212> DNA

<213> Homo sapiens

<400> 8

atactgcaga	ggtctctggt	gcatgtgtgt	atgtgtgctg	ttgtgtgtgt	ttgtgtgtct	60
gtgtgtttctg	ccccagtgag	actgcagccc	ttgtaaatac	tttgacacct	tttgcaagaa	120
ggaatctgaa	caattgcaac	tgaaggcaca	ttgttatcat	ctcgtctttg	ggtgatgctg	180
ttcctcactg	cagatggata	attttccttt	taatcaggaa	tttcatatgc	agaataaatg	240
gtaattaaaa	tgtgcaggat	gacaagatgg	agcaaacagt	gcttgtacca	ccaggacctg	300
acagcttcaa	cttcttcacc	agagaatctc	ttgcggctat	tgaaagacgc	attgcagaag	360
aaaaggcaaa	gaatcccaaa	ccagacaaaa	aagatgacga	cgaaaatggc	ccaaagccaa	420
atagtgaactt	ggaagctgga	aagaaccttc	catttattta	tggagacatt	cctccagaga	480
tggtgtcaga	gcccctggag	gacctggacc	cctactatat	caataagaaa	acttttatag	540
tattgaataa	attgaaggcc	atcttccggg	tcagtgccac	ctctgccctg	tacattttta	600
ctcccttcaa	tcctcttagg	aaaatagcta	ttaagatttt	ggtacattca	ttattcagca	660
tgctaattat	gtgcactatt	ttgacaaact	gtgtgtttat	gacaatgagt	aaccctcctg	720
attggacaaa	gaatgtagaa	tacaccttca	caggaatata	tacttttgaa	tcacttataa	780
aaattattgc	aaggggattc	tgtttagaag	attttacttt	ccttcgggat	ccatggaact	840
ggctcgattt	cactgtcatt	acatttgctg	acgtcacaga	gtttgtggac	ctgggcaatg	900
tctcggcatt	gagaacattc	agagttctcc	gagcattgaa	gacgatttca	gtcattccag	960
gcctgaaaac	cattgtggga	gccctgatcc	agtctgtgaa	gaagctctca	gatgtaatga	1020
tcctgactgt	gttctgtctg	agcgtatttg	ctctaattgg	gctgcagctg	ttcatgggca	1080
acctgaggaa	taaatgtata	caatggcctc	ccaccaatgc	ttccttggag	gaacatagta	1140
tagaaaagaa	tataactgtg	aattataatg	gtacacttat	aatgaaact	gtctttgagt	1200
ttgactggaa	gtcatatatt	caagattcaa	gatataatta	tttcctggag	ggttttttag	1260
atgcactact	atgtggaaat	agctctgatg	caggccaatg	tccagaggga	tatatgtgtg	1320
tgaaagctgg	tagaaatccc	aattatggct	acacaagctt	tgataccttc	agttgggctt	1380
ttttgtcctt	gtttcgacta	atgactcagg	acttctggga	aatcttttat	caactgacat	1440
tacgtgctgc	tgggaaaacg	tacatgatat	tttttgtatt	ggtcattttc	ttgggctcat	1500
tctaccta	aaatttgatc	ctggctgtgg	tggccatggc	ctacgaggaa	cagaatcagg	1560
ccaccttgg	agaagcagaa	cagaaagagg	ccgaatttca	gcagatgatt	gaacagctta	1620
aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcctcagaa	cattccagag	1680
agcccagtg	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgtctaa	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctgggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aagggttttcg	cttctccatt	gaagggaacc	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atcogtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagcttttaga	gggcgagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtgtt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtgggtt	2220
ccttggttgg	tggaccttca	gttccctacat	cgcctgttgg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaagggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacia	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttgg	tataaatttt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattgggt	aaaagtga	catgttgtca	acctgggtgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaataa	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttcact	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcc	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggttt	attgtgacgc	ttagcctggg	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaat	2880
cttggccaac	gttaaatatg	ctaataaaga	tcacgcggca	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcatttttgc	cgtggctggc	atgcagctct	3000
ttggtaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtgtt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgccgggtca	agccatgtgc	cttactgtct	3180
tcatgatgg	catggtgatt	ggaaacctag	tggtcctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgacg	ccactgatga	tgataatgaa	atgaataatc	3300

tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aattttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagtcctta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaattttaac	acggaagact	3660
ttagtagtga	atcggatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaatatgc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tatttcacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaactctct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggg	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatatctctg	ctaattttca	gcacatggg	cgtaaatttg	tttgctggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatgggtctt	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atgggtggaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctatttac	tggagagtgt	gtactgaaac	5040
tcatctctct	acgccattat	tattttacca	ttggatggaa	tatttttgat	tttgtgggtg	5100
tcattctctc	cattgtaggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160
ctaccctgtt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttctt	gcgttgttta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcatctacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatggt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgactgtg	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttctt	ggttgtgggtg	aacatgtaca	tgcggtcat	cctggagaac	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgaggttt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcatggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaacccaa	caaactccag	ctcattgcca	5820
tggatttgcc	catggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaagggtct	cctatcagcc	aatcactact	actttaaaac	6000
gaaaacaaga	ggaagtatct	gctgtcatta	ttcagcgtgc	ttacagacgc	caccttttaa	6060
agcgaactgt	aaaacaagct	tcctttacgt	acaataaaaa	caaaatcaaa	ggtggggcta	6120
atcttcttat	aaaagaagac	atgataattg	acagaataaa	tgaaaactct	attacagaaa	6180
aaactgatct	gaccatgtcc	actgcagctt	gtccaccttc	ctatgaccgg	gtgacaaagc	6240
caattgtgga	aaaacatgag	caagaaggca	aagatgaaaa	agccaaaggg	aaataaatga	6300
aaataaataa	aaataattgg	gtgacaaatt	gtttacagcc	tgtgaagggtg	atgtattttt	6360
atcaacagga	ctccttttagg	aggtcaatgc	caaactgact	gttttttacac	aatctcctt	6420
aaggtcagtg	cctacaataa	gacagtgacc	ccttgtcagc	aaactgtgac	tctgtgtaaa	6480
ggggagatga	ccttgacagg	aggttactgt	tctcactacc	agctgacact	gctgaagata	6540
agatgcacaa	tggctagtca	gactgtaggg	accagtttca	aggggtgcaa	acctgtgatt	6600
ttgggggttg	ttaacatgaa	acacttttagt	gtagtaattg	tatccactgt	ttgcatttca	6660
actgccacat	ttgtcacatt	tttatggaa	ctgttagtgg	attcatcttt	ttgttaatcc	6720
atgtgtttat	tatatgtgac	tatttttgta	aacgaagttt	ctgttgagaa	ataggctaag	6780
gacctctata	acaggtatgc	cacctggggg	gtatggcaac	cacatggccc	tcccagctac	6840
acaaagtcgt	ggtttgcagt	agggcatgct	gcacttagag	atcatgcatg	agaaaaagtc	6900

acaagaaaaa	caaattctta	aatttcacca	tatttctggg	aggggtaatt	gggtgataag	6960
tggagggtgct	ttgttgatct	tgttttgcga	aatccagccc	ctagaccaag	tagattatth	7020
gtgggtaggc	cagtaaactc	tagcagggtg	aaacttcatt	caaagtgttg	gagtcataaa	7080
tgttatgttt	ctttttgttg	tattaaaaaa	aaaacctgaa	tagtgaatat	tgccccctac	7140
cctccaccgc	cagaagactg	aattgaccaa	aattactctt	tataaatttc	tgctttttcc	7200
tgcaactttgt	ttagccatct	ttgggctctc	agcaagggtg	acactgtata	tgttaatgaa	7260
atgctattta	ttatgtaaat	agtcatttta	ccctgtgggtg	cacgtttgag	caaacaaata	7320
atgacctaag	cacagtatth	attgcatcaa	atatgtacca	caagaaatgt	agagtgcagg	7380
ctttacacag	gtaataaaat	gtattctgta	ccatttatag	atagtttgga	tgctatcaat	7440
gcatgtttat	attaccatgc	tgctgtatct	ggtttctctc	actgctcaga	atctcattta	7500
tgagaaacca	tatgtcagtg	gtaaagtcaa	ggaaattggt	caacagatct	catttatth	7560
agtcattaag	caatagtgtg	cagcacttta	acagcttttt	ggttatthtt	acattthtaag	7620
tggataacat	atggtatata	gccagactgt	acagacatgt	ttaaaaaac	acactgctta	7680
acctattaaa	tatgtgttta	gaattttata	agcaaatata	aatactgtaa	aaagtcactt	7740
tattttatth	ttcagcatta	tgtacataaa	tatgaagagg	aaattatctt	caggttgata	7800
tcacaatcac	ttttcttact	ttctgtccat	agtacttttt	catgaaagaa	atttgctaaa	7860
taagacatga	aaacaagact	gggtagttgt	agatttctgc	tttttaaatt	acatttgcta	7920
atttttagatt	atttcacaat	tttaaggagc	aaaatagggt	cacgattcat	atccaaatta	7980
tgctttgcaa	ttggaaaagg	gtttaaaatt	ttatttatat	ttctggtagt	acctgtacta	8040
actgaattga	aggtagtgct	tatgttatth	ttgttctttt	tttctgactt	cggtttatgt	8100
tttcatttct	ttggagtaat	gctgctctag	attgttctaa	atagaatgtg	ggcttcataa	8160
tttttttttc	cacaaaaaca	gagtagtcaa	cttatatagt	caattacatc	aggacattth	8220
gtgtttctta	cagaagcaaa	ccataggctc	ctcttttctt	taaaactact	tagataaact	8280
gtattcgtga	actgcatgct	ggaaaatgct	actattatgc	taaataatgc	taaccaacat	8340
ttaaaatgtg	caaaactaat	aaagattaca	ttttttatth	t		8381

<210> 9

<211> 8381

<212> DNA

<213> Homo sapiens

<400> 9

atactgcaga	ggctctctgg	gcatgtgtgt	atgtgtgcgt	ttgtgtgtgt	ttgtgtgtct	60
gtgtgttctg	ccccagtgag	actgcagccc	ttgtaaatac	tttgacacct	tttgcaagaa	120
ggaatctgaa	caattgcaac	tgaaggcaca	ttgttatcat	ctcgtctttg	ggatgatgctg	180
ttctcactg	cagatggata	attttcctth	taatcaggaa	tttcatatgc	agaataaatg	240
gtaattaaaa	tgtgcaggat	gacaagatgg	agcaaacagt	gcttgtagca	ccaggacctg	300
acagcttcaa	cttcttcacc	agagaatctc	ttgcggctat	tgaaagacgc	attgcagaag	360
aaaaggcaaa	gaatcccaaa	ccagacaaaa	aagatgacga	cgaaaatggc	ccaaagccaa	420
atagtgaact	ggaagctgga	aagaaccttc	catttatth	tggagacatt	cctccagaga	480
tggtgtcaga	gcccctggag	gacctggacc	cctactatat	caataagaaa	acttttatag	540
tattgaataa	attgaaggcc	atcttccggg	tcagtgccac	ctctgccctg	tacattthta	600
ctcccttcaa	tcctcttagg	aaaatagcta	ttaagattth	ggtacattca	ttattcagca	660
tgctaattat	gtgcaactat	ttgacaaact	gtgtgtttat	gacaatgagt	aacctcctg	720
attggacaaa	gaatgtagaa	tacaccttca	caggaatata	tacttttgaa	tcacttataa	780
aaattattgc	aaggggattc	tgtttagaag	attttactth	ccttcgggat	ccatggaact	840
ggctcgattt	cactgtcatt	acatttgctg	acgtcacaga	gtttgtggac	ctgggcaatg	900
tctcggcatt	gagaacattc	agagttctcc	gagcattgaa	gacgatttca	gtcattccag	960
gcctgaaaac	cattgtggga	gccctgatcc	agtctgtgaa	gaagctctca	gatgtaatga	1020
tcctgactgt	gttctgtctg	agcgtatttg	ctctaattgg	gctgcagctg	ttcatgggca	1080
acctgaggaa	taaatgtata	caatggcctc	ccaccaatgc	ttccttggag	gaacatagta	1140
tagaaaagaa	tataactgtg	aattataatg	gtacacttat	aaatgaaact	gtctttgagt	1200
ttgactggaa	gtcatatatt	caagattcaa	gatatcatta	tttcctggag	ggtttttttag	1260
atgcactact	atgtggaaat	agctctgatg	caggccaatg	tccagaggga	tatatgtgtg	1320
tgaaagctgg	tagaaatccc	aattatggct	acacaagctt	tgataccttc	agttgggctt	1380
ttttgtcctt	gtttcgacta	atgactcagg	acttctggga	aaatctttat	caactgacat	1440
tacgtgctgc	tgggaaaacg	tacatgatat	tttttgtatt	ggtcattttc	ttgggctcat	1500
tctacctaat	aaatttgatc	ctggctgtgg	tggccatggc	ctacgaggaa	cagaatcagg	1560
ccaccttgga	agaagcagaa	cagaaagagg	ccgaatttca	gcagatgatt	gaacagctta	1620

aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcctcagaa	cattccagag	1680
agcccagtgc	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgctaa	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aagggttttcg	cttctccatt	gaagggaacc	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atccgtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagctttaga	gggcgagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtggt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtggttt	2220
ccttggttgg	tggaccttca	gttccctacat	cgcctgttgg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaagggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacaa	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttgg	tataaatttt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattgggt	aaaagtgaaa	catgttgtca	acctggttgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaataa	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttctact	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggtttt	attgtgacgc	ttagcctggt	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaatatg	ctaataaaga	tcacgggcaa	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcatttttgc	cgtggtcggc	atgcagctct	3000
ttggtaaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgatttgtgt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcatgatggt	catggtgatt	ggaaacctag	tggtcctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgacg	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aatttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacagcagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagtctta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaattttaa	acggaagact	3660
ttagtagtga	atcggatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtgggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaaatatgc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tattttacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaactctct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggt	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatatcttgg	ctaattttca	gcatcatggg	cgtaaatttg	tttgcaggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatggtcct	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctattttac	tggagagtgt	gtactgaaac	5040
tcactctctct	acgccattat	tattttacca	ttggatggaa	tatttttgat	tttgtggttg	5100
tcattctctc	cattgtagggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160

ctaccctggt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttcct	gcgttggtta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcacttacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatgtt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgactgtg	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttcct	ggttgtggtg	aacatgtaca	tcgcggtcat	cctggagaac	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgagggtt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcattggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaaccaa	caaactccag	ctcattgcca	5820
tggatttgcc	catggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaaggctc	cctatcagcc	aatcactact	actttaaaac	6000
gaaaacaaga	ggaagtatct	gctgtcatta	ttcagcgtgc	ttacagacgc	caccttttaa	6060
agcgaactgt	aaaacaagct	tcctttacgt	acaataaaaa	caaaatcaaa	ggtggggcta	6120
atcttcttat	aaaagaagac	atgataattg	acagaataaa	tgaaaactct	attacagaaa	6180
aaactgatct	gaccatgtcc	actgcagctt	gtccaccttc	ctatgaccgg	gtgacaaagc	6240
caattgtgga	aaaacatgag	caagaaggca	aagatgaaaa	agccaaaggg	aaataaatga	6300
aaataaataa	aaataattgg	gtgacaaatt	gtttacagcc	tgtgaagggtg	atgtattttt	6360
atcaacagga	ctcctttagg	aggtcaatgc	caaactgact	gttttttacac	aaatctcctt	6420
aaggtcagtg	cctacaataa	gacagtgacc	ccttgtcagc	aaactgtgac	tctgtgtaaa	6480
ggggagatga	ccttgacagg	aggttactgt	tctcactacc	agctgacact	gctgaagata	6540
agatgcacaa	tggctagtca	gactgtaggg	accagtttca	aggggtgcaa	acctgtgatt	6600
ttgggggtgt	ttaacatgaa	acactttagt	gtagtaattg	tatccactgt	ttgcattttca	6660
actgccacat	ttgtcacatt	tttatggaat	ctgttagtggt	attcatcttt	ttgttaatcc	6720
atgtgtttat	tatatgtgac	tattttttgta	aacgaagttt	ctgttgagaa	ataggctaag	6780
gacctctata	acaggatgac	cacctggggg	gtatggcaac	cacatggccc	tcccagctac	6840
acaaagtcgt	ggtttgcatg	agggcatgct	gcacttagag	atcatgcatg	agaaaaagtc	6900
acaagaaaaa	caaattctta	aatttcacca	tattttctggg	aggggttaatt	gggtgataag	6960
tggaggtgct	ttgttgatct	tgtttttgca	aatccagccc	ctagaccaag	tagattattt	7020
gtgggtaggc	cagtaaatct	tagcagggtg	aaacttcatt	caaagtgttg	gagtcataaa	7080
tgttatgttt	ctttttgttg	tattaaaaaa	aaaacctgaa	tagtgaatat	tgccctcac	7140
cctccaccgc	cagaagactg	aattgaccaa	aattactctt	tataaatttc	tgctttttcc	7200
tgcactttgt	ttagccatct	ttgggctctc	agcaagggtg	acactgtata	tgttaatgaa	7260
atgctattta	ttatgtaaat	agtcattttta	ccctgtgggtg	cacgtttgag	caaacaaata	7320
atgacctaa	cacagtatct	attgcatcaa	atatgtacca	caagaaatgt	agagtgcag	7380
ctttacacag	gtaataaaat	gtattctgta	ccatttatag	atagtttgga	tgctatcaat	7440
gcatgtttat	attaccatgc	tgctgtatct	ggtttctctc	actgctcaga	atctcattta	7500
tgagaaacca	tatgtcagtg	gtaaaagtcaa	ggaaattgtt	caacagatct	cattttattta	7560
agtcattaag	caatagtttg	cagcacttta	acagcttttt	ggttattttt	acattttaag	7620
tggataacat	atggtatata	gccagactgt	acagacatgt	ttaaaaaaac	acactgctta	7680
acctattaaa	tatgtgttta	gaattttata	agcaaataata	aatactgtaa	aaagtcactt	7740
tattttatatt	ttcagcatta	tgtacataaa	tatgaagagg	aaattatctt	caggttgata	7800
tcacaatcac	ttttcttact	ttctgtccat	agtacttttt	catgaaagaa	atttgctaaa	7860
taagacatga	aaacaagact	gggtagttgt	agattttctgc	tttttaaatt	acatttgcta	7920
attttagatt	atttcacaa	tttaaggagc	aaaatagggt	cacgattcat	atccaaatta	7980
tgctttgcaa	ttggaaaagg	gtttaaaatt	ttattttatat	ttctggtagt	acctgtacta	8040
actgaattga	aggtagtgt	tatgttatct	ttgttctttt	ttctgactt	cggtttatgt	8100
tttcatttct	ttggagtaat	gctgctctag	attgttctaa	atagaatgtg	ggcttcataa	8160
tttttttttc	cacaaaaaca	gagtagtcaa	cttatatagt	caattacatc	aggacatttt	8220
gtgtttctta	cagaagcaaa	ccataggctc	ctcttttctc	taaaactact	tagataaact	8280
gtattcgtga	actgcatgct	ggaaaatgct	actattatgc	taaataatgc	taaccaacat	8340
ttaaaatgtg	caaaactaat	aaagattaca	ttttttatct	t		8381

<210> 10
 <211> 2009
 <212> PRT
 <213> Homo sapiens

```

<400> 10
Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe
1      5      10      15
Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu
20      25      30
Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly
35      40      45
Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
50      55      60
Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
65      70      75      80
Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu
85      90      95
Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
100     105     110
Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser
115     120     125
Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
130     135     140
Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145     150     155     160
Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg
165     170     175
Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
180     185     190
Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp
195     200     205
Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
210     215     220
Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225     230     235     240
Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
245     250     255
Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
260     265     270
Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu
275     280     285
Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu
290     295     300
Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp
305     310     315     320
Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys
325     330     335
Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val
340     345     350
Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe
355     360     365
Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp
370     375     380
Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met
385     390     395     400
Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn
405     410     415
Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala
420     425     430
Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile
435     440     445
Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala
450     455     460

```

Thr	Ala	Ser	Glu	His	Ser	Arg	Glu	Pro	Ser	Ala	Ala	Gly	Arg	Leu	Ser	465	470	475	480
Asp	Ser	Ser	Ser	Glu	Ala	Ser	Lys	Leu	Ser	Ser	Lys	Ser	Ala	Lys	Glu				
				485					490					495					
Arg	Arg	Asn	Arg	Arg	Lys	Lys	Arg	Lys	Gln	Lys	Glu	Gln	Ser	Gly	Gly	500	505	510	
Glu	Glu	Lys	Asp	Glu	Asp	Glu	Phe	Gln	Lys	Ser	Glu	Ser	Glu	Asp	Ser	515	520	525	
Ile	Arg	Arg	Lys	Gly	Phe	Arg	Phe	Ser	Ile	Glu	Gly	Asn	Arg	Leu	Thr	530	535	540	
Tyr	Glu	Lys	Arg	Tyr	Ser	Ser	Pro	His	Gln	Ser	Leu	Leu	Ser	Ile	Arg	545	550	555	560
Gly	Ser	Leu	Phe	Ser	Pro	Arg	Arg	Asn	Ser	Arg	Thr	Ser	Leu	Phe	Ser	565	570	575	
Phe	Arg	Gly	Arg	Ala	Lys	Asp	Val	Gly	Ser	Glu	Asn	Asp	Phe	Ala	Asp	580	585	590	
Asp	Glu	His	Ser	Thr	Phe	Glu	Asp	Asn	Glu	Ser	Arg	Arg	Asp	Ser	Leu	595	600	605	
Phe	Val	Pro	Arg	Arg	His	Gly	Glu	Arg	Arg	Asn	Ser	Asn	Leu	Ser	Gln	610	615	620	
Thr	Ser	Arg	Ser	Ser	Arg	Met	Leu	Ala	Val	Phe	Pro	Ala	Asn	Gly	Lys	625	630	635	640
Met	His	Ser	Thr	Val	Asp	Cys	Asn	Gly	Val	Val	Ser	Leu	Val	Gly	Gly	645	650	655	
Pro	Ser	Val	Pro	Thr	Ser	Pro	Val	Gly	Gln	Leu	Leu	Pro	Glu	Val	Ile	660	665	670	
Ile	Asp	Lys	Pro	Ala	Thr	Asp	Asp	Asn	Gly	Thr	Thr	Thr	Glu	Thr	Glu	675	680	685	
Met	Arg	Lys	Arg	Arg	Ser	Ser	Ser	Phe	His	Val	Ser	Met	Asp	Phe	Leu	690	695	700	
Glu	Asp	Pro	Ser	Gln	Arg	Gln	Arg	Ala	Met	Ser	Ile	Ala	Ser	Ile	Leu	705	710	715	720
Thr	Asn	Thr	Val	Glu	Glu	Leu	Glu	Glu	Ser	Arg	Gln	Lys	Cys	Pro	Pro	725	730	735	
Cys	Trp	Tyr	Lys	Phe	Ser	Asn	Ile	Phe	Leu	Ile	Trp	Asp	Cys	Ser	Pro	740	745	750	
Tyr	Trp	Leu	Lys	Val	Lys	His	Val	Val	Asn	Leu	Val	Val	Met	Asp	Pro	755	760	765	
Phe	Val	Asp	Leu	Ala	Ile	Thr	Ile	Cys	Ile	Val	Leu	Asn	Thr	Leu	Phe	770	775	780	
Met	Ala	Met	Glu	His	Tyr	Pro	Met	Thr	Asp	His	Phe	Asn	Asn	Val	Leu	785	790	795	800
Thr	Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Phe	805	810	815	
Leu	Lys	Ile	Ile	Ala	Met	Asp	Pro	Tyr	Tyr	Tyr	Phe	Gln	Glu	Gly	Trp	820	825	830	
Asn	Ile	Phe	Asp	Gly	Phe	Ile	Val	Thr	Leu	Ser	Leu	Val	Glu	Leu	Gly	835	840	845	
Leu	Ala	Asn	Val	Glu	Gly	Leu	Ser	Val	Leu	Arg	Ser	Phe	Arg	Leu	Leu	850	855	860	
Arg	Val	Phe	Lys	Leu	Ala	Lys	Ser	Trp	Pro	Thr	Leu	Asn	Met	Leu	Ile	865	870	875	880
Lys	Ile	Ile	Gly	Asn	Ser	Val	Gly	Ala	Leu	Gly	Asn	Leu	Thr	Leu	Val	885	890	895	
Leu	Ala	Ile	Ile	Val	Phe	Ile	Phe	Ala	Val	Val	Gly	Met	Gln	Leu	Phe	900	905	910	
Gly	Lys	Ser	Tyr	Lys	Asp	Cys	Val	Cys	Lys	Ile	Ala	Ser	Asp	Cys	Gln	915	920	925	

Leu	Pro	Arg	Trp	His	Met	Asn	Asp	Phe	Phe	His	Ser	Phe	Leu	Ile	Val
930						935					940				
Phe	Arg	Val	Leu	Cys	Gly	Glu	Trp	Ile	Glu	Thr	Met	Trp	Asp	Cys	Met
945					950					955					960
Glu	Val	Ala	Gly	Gln	Ala	Met	Cys	Leu	Thr	Val	Phe	Met	Met	Val	Met
				965					970					975	
Val	Ile	Gly	Asn	Leu	Val	Val	Leu	Asn	Leu	Phe	Leu	Ala	Leu	Leu	Leu
			980					985					990		
Ser	Ser	Phe	Ser	Ala	Asp	Asn	Leu	Ala	Ala	Thr	Asp	Asp	Asp	Asn	Glu
		995					1000					1005			
Met	Asn	Asn	Leu	Gln	Ile	Ala	Val	Asp	Arg	Met	His	Lys	Gly	Val	
1010						1015					1020				
Ala	Tyr	Val	Lys	Arg	Lys	Ile	Tyr	Glu	Phe	Ile	Gln	Gln	Ser	Phe	
1025						1030					1035				
Ile	Arg	Lys	Gln	Lys	Ile	Leu	Asp	Glu	Ile	Lys	Pro	Leu	Asp	Asp	
1040						1045					1050				
Leu	Asn	Asn	Lys	Lys	Asp	Ser	Cys	Met	Ser	Asn	His	Thr	Ala	Glu	
1055						1060					1065				
Ile	Gly	Lys	Asp	Leu	Asp	Tyr	Leu	Lys	Asp	Val	Asn	Gly	Thr	Thr	
1070						1075					1080				
Ser	Gly	Ile	Gly	Thr	Gly	Ser	Ser	Val	Glu	Lys	Tyr	Ile	Ile	Asp	
1085						1090					1095				
Glu	Ser	Asp	Tyr	Met	Ser	Phe	Ile	Asn	Asn	Pro	Ser	Leu	Thr	Val	
1100						1105					1110				
Thr	Val	Pro	Ile	Ala	Val	Gly	Glu	Ser	Asp	Phe	Glu	Asn	Leu	Asn	
1115						1120					1125				
Thr	Glu	Asp	Phe	Ser	Ser	Glu	Ser	Asp	Leu	Glu	Glu	Ser	Lys	Glu	
1130						1135					1140				
Lys	Leu	Asn	Glu	Ser	Ser	Ser	Ser	Ser	Glu	Gly	Ser	Thr	Val	Asp	
1145						1150					1155				
Ile	Gly	Ala	Pro	Val	Glu	Glu	Gln	Pro	Val	Val	Glu	Pro	Glu	Glu	
1160						1165					1170				
Thr	Leu	Glu	Pro	Glu	Ala	Cys	Phe	Thr	Glu	Gly	Cys	Val	Gln	Arg	
1175						1180					1185				
Phe	Lys	Cys	Cys	Gln	Ile	Asn	Val	Glu	Glu	Gly	Arg	Gly	Lys	Gln	
1190						1195					1200				
Trp	Trp	Asn	Leu	Arg	Arg	Thr	Cys	Phe	Arg	Ile	Val	Glu	His	Asn	
1205						1210					1215				
Trp	Phe	Glu	Thr	Phe	Ile	Val	Phe	Met	Ile	Leu	Leu	Ser	Ser	Gly	
1220						1225					1230				
Ala	Leu	Ala	Phe	Glu	Asp	Ile	Tyr	Ile	Asp	Gln	Arg	Lys	Thr	Ile	
1235						1240					1245				
Lys	Thr	Met	Leu	Glu	Tyr	Ala	Asp	Lys	Val	Phe	Thr	Tyr	Ile	Phe	
1250						1255					1260				
Ile	Leu	Glu	Met	Leu	Leu	Lys	Trp	Val	Ala	Tyr	Gly	Tyr	Gln	Thr	
1265						1270					1275				
Tyr	Phe	Thr	Asn	Ala	Trp	Cys	Trp	Leu	Asp	Phe	Leu	Ile	Val	Asp	
1280						1285					1290				
Val	Ser	Leu	Val	Ser	Leu	Thr	Ala	Asn	Ala	Leu	Gly	Tyr	Ser	Glu	
1295						1300					1305				
Leu	Gly	Ala	Ile	Lys	Ser	Leu	Arg	Thr	Leu	Arg	Ala	Leu	Arg	Pro	
1310						1315					1320				
Leu	Arg	Ala	Leu	Ser	Arg	Phe	Glu	Gly	Met	Arg	Val	Val	Val	Asn	
1325						1330					1335				
Ala	Leu	Leu	Gly	Ala	Ile	Pro	Ser	Ile	Met	Asn	Val	Leu	Leu	Val	
1340						1345					1350				
Cys	Leu	Ile	Phe	Trp	Leu	Ile	Phe	Ser	Ile	Met	Gly	Val	Asn	Leu	
1355						1360					1365				

Phe	Ala	Gly	Lys	Phe	Tyr	His	Cys	Ile	Asn	Thr	Thr	Thr	Gly	Asp
1370						1375						1380		
Arg	Phe	Asp	Ile	Glu	Asp	Val	Asn	Asn	His	Thr	Asp	Cys	Leu	Lys
1385						1390						1395		
Leu	Ile	Glu	Arg	Asn	Glu	Thr	Ala	Arg	Trp	Lys	Asn	Val	Lys	Val
1400						1405						1410		
Asn	Phe	Asp	Asn	Val	Gly	Phe	Gly	Tyr	Leu	Ser	Leu	Leu	Gln	Val
1415						1420						1425		
Ala	Thr	Phe	Lys	Gly	Trp	Met	Asp	Ile	Met	Tyr	Ala	Ala	Val	Asp
1430						1435						1440		
Ser	Arg	Asn	Val	Glu	Leu	Gln	Pro	Lys	Tyr	Glu	Lys	Ser	Leu	Tyr
1445						1450						1455		
Met	Tyr	Leu	Tyr	Phe	Val	Ile	Phe	Ile	Ile	Phe	Gly	Ser	Phe	Phe
1460						1465						1470		
Thr	Leu	Asn	Leu	Phe	Ile	Gly	Val	Ile	Ile	Asp	Asn	Phe	Asn	Gln
1475						1480						1485		
Gln	Lys	Lys	Lys	Phe	Gly	Gly	Gln	Asp	Ile	Phe	Met	Thr	Glu	Glu
1490						1495						1500		
Gln	Lys	Lys	Tyr	Tyr	Asn	Ala	Met	Lys	Lys	Leu	Gly	Ser	Lys	Lys
1505						1510						1515		
Pro	Gln	Lys	Pro	Ile	Pro	Arg	Pro	Gly	Asn	Lys	Phe	Gln	Gly	Met
1520						1525						1530		
Val	Phe	Asp	Phe	Val	Thr	Arg	Gln	Val	Phe	Asp	Ile	Ser	Ile	Met
1535						1540						1545		
Ile	Leu	Ile	Cys	Leu	Asn	Met	Val	Thr	Met	Met	Val	Glu	Thr	Asp
1550						1555						1560		
Asp	Gln	Ser	Glu	Tyr	Val	Thr	Thr	Ile	Leu	Ser	Arg	Ile	Asn	Leu
1565						1570						1575		
Val	Phe	Ile	Val	Leu	Phe	Thr	Gly	Glu	Cys	Val	Leu	Lys	Leu	Ile
1580						1585						1590		
Ser	Leu	Arg	His	Tyr	Tyr	Phe	Thr	Ile	Gly	Trp	Asn	Ile	Phe	Asp
1595						1600						1605		
Phe	Val	Val	Val	Ile	Leu	Ser	Ile	Val	Gly	Met	Phe	Leu	Ala	Glu
1610						1615						1620		
Leu	Ile	Glu	Lys	Tyr	Phe	Val	Ser	Pro	Thr	Leu	Phe	Arg	Val	Ile
1625						1630						1635		
Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Lys	Gly	Ala
1640						1645						1650		
Lys	Gly	Ile	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser	Leu	Pro
1655						1660						1665		
Ala	Leu	Phe	Asn	Ile	Gly	Leu	Leu	Leu	Phe	Leu	Val	Met	Phe	Ile
1670						1675						1680		
Tyr	Ala	Ile	Phe	Gly	Met	Ser	Asn	Phe	Ala	Tyr	Val	Lys	Arg	Glu
1685						1690						1695		
Val	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Glu	Thr	Phe	Gly	Asn	Ser
1700						1705						1710		
Met	Ile	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp	Asp	Gly
1715						1720						1725		
Leu	Leu	Ala	Pro	Ile	Leu	Asn	Ser	Lys	Pro	Pro	Asp	Cys	Asp	Pro
1730						1735						1740		
Asn	Lys	Val	Asn	Pro	Gly	Ser	Ser	Val	Lys	Gly	Asp	Cys	Gly	Asn
1745						1750						1755		
Pro	Ser	Val	Gly	Ile	Phe	Phe	Phe	Val	Ser	Tyr	Ile	Ile	Ile	Ser
1760						1765						1770		
Phe	Leu	Val	Val	Val	Asn	Met	Tyr	Ile	Ala	Val	Ile	Leu	Glu	Asn
1775						1780						1785		
Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Ala	Glu	Pro	Leu	Ser	Glu	Asp
1790						1795						1800		

Asp	Phe	Glu	Met	Phe	Tyr	Glu	Val	Trp	Glu	Lys	Phe	Asp	Pro	Asp	
1805						1810					1815				
Ala	Thr	Gln	Phe	Met	Glu	Phe	Glu	Lys	Leu	Ser	Gln	Phe	Ala	Ala	
1820						1825					1830				
Ala	Leu	Glu	Pro	Pro	Leu	Asn	Leu	Pro	Gln	Pro	Asn	Lys	Leu	Gln	
1835						1840					1845				
Leu	Ile	Ala	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile	His	
1850						1855					1860				
Cys	Leu	Asp	Ile	Leu	Phe	Ala	Phe	Thr	Lys	Arg	Val	Leu	Gly	Glu	
1865						1870					1875				
Ser	Gly	Glu	Met	Asp	Ala	Leu	Arg	Ile	Gln	Met	Glu	Glu	Arg	Phe	
1880						1885					1890				
Met	Ala	Ser	Asn	Pro	Ser	Lys	Val	Ser	Tyr	Gln	Pro	Ile	Thr	Thr	
1895						1900					1905				
Thr	Leu	Lys	Arg	Lys	Gln	Glu	Glu	Val	Ser	Ala	Val	Ile	Ile	Gln	
1910						1915					1920				
Arg	Ala	Tyr	Arg	Arg	His	Leu	Leu	Lys	Arg	Thr	Val	Lys	Gln	Ala	
1925						1930					1935				
Ser	Phe	Thr	Tyr	Asn	Lys	Asn	Lys	Ile	Lys	Gly	Gly	Ala	Asn	Leu	
1940						1945					1950				
Leu	Ile	Lys	Glu	Asp	Met	Ile	Ile	Asp	Arg	Ile	Asn	Glu	Asn	Ser	
1955						1960					1965				
Ile	Thr	Glu	Lys	Thr	Asp	Leu	Thr	Met	Ser	Thr	Ala	Ala	Cys	Pro	
1970						1975					1980				
Pro	Ser	Tyr	Asp	Arg	Val	Thr	Lys	Pro	Ile	Val	Glu	Lys	His	Glu	
1985						1990					1995				
Gln	Glu	Gly	Lys	Asp	Glu	Lys	Ala	Lys	Gly	Lys					
2000						2005									

<210> 11
 <211> 8381
 <212> DNA
 <213> Homo sapiens

<400> 11

atactgcaga	ggctctctggt	gcatgtgtgt	atgtgtgcgt	ttgtgtgtgt	ttgtgtgtct	60
gtgtgttctg	ccccagttag	actgcagccc	ttgttaaatac	tttgacacct	tttgcaagaa	120
ggaatctgaa	caattgcaac	tgaaggcaca	ttgttatcat	ctcgtctttg	ggatgatgctg	180
ttcctcactg	cagatggata	attttccttt	taatcaggaa	tttcatatgc	agaataaatg	240
gtaattaaaa	tgtgcaggat	gacaagatgg	agcaaacagt	gcttgtacca	ccaggacctg	300
acagcttcaa	cttcttcacc	agagaatctc	ttgcggctat	tgaaagacgc	attgcagaag	360
aaaaggcaaa	gaatcccaaa	ccagacaaaa	aagatgacga	cgaaaatggc	ccaaagccaa	420
atagtgactt	ggaagctgga	aagaaccttc	catttatatta	tggagacatt	cctccagaga	480
tggtgtcaga	gcccctggag	gacctggacc	cctactatat	caataagaaa	acttttatag	540
tattgaataa	attgaaggcc	atcttcgggt	tcagtgccac	ctctgccctg	tacattttta	600
ctcccttcaa	tcctcttagg	aaaatagcta	ttaagatttt	ggtacattca	ttattcagca	660
tgctaattat	gtgcactatt	ttgacaaact	gtgtgtttat	gacaatgagt	aaccctcctg	720
attggacaaa	gaatgtagaa	tacaccttca	caggaatata	tacttttgaa	tcacttataa	780
aaattattgc	aaggggattc	tgtttagaag	attttacttt	ccttcgggat	ccatggaact	840
ggctcgattt	cactgtcatt	acatttgcgt	acgtcacaga	gtttgtggac	ctgggcaatg	900
tctcggcatt	gagaacattc	agagttctcc	gagcattgaa	gacgatttca	gtcattccag	960
gcctgaaaac	cattgtggga	gccctgatcc	agtctgtgaa	gaagctctca	gatgtaatga	1020
tcctgactgt	gttctgtctg	agcgtatttg	ctctaattgg	gctgcagctg	ttcatgggca	1080
acctgaggaa	taaatgtata	caatggcctc	ccaccaatgc	ttccttggag	gaacatagta	1140
tagaaaagaa	tataactgtg	aattataatg	gtacacttat	aaatgaaact	gtctttgagt	1200
ttgactggaa	gtcatatatt	caagattcaa	gatataatta	tttcttggag	ggtttttttag	1260
atgcactact	atgtggaaat	agctctgatg	caggccaatg	tccagaggga	tatatgtgtg	1320
tgaaagctgg	tagaaatccc	aattatggct	acacaagctt	tgataccttc	agttgggctt	1380
ttttgtcctt	gtttcgacta	atgactcagg	acttctggga	aaatctttat	caactgacat	1440

tacgtgctgc	tgggaaaacg	tacatgatata	tttttgtatt	ggtcattttc	ttgggctcat	1500
tctacctaata	aaattttgatc	ctggctgtgg	tggccatggc	ctacgaggaa	cagaatcagg	1560
ccaccttgga	agaagcagaa	cagaaagagg	ccgaattttca	gcagatgatt	gaacagctta	1620
aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcctcagaa	cattccagag	1680
agcccagtg	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgtctaa	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aaggtttttcg	cttctccatt	gaagggaacc	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atccgtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagcttttaga	gggagagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtggt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtggttt	2220
ccttggttg	tggaccttca	gttcctacat	cgctgttg	acagcttctg	ccagagggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaagggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacaa	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttg	tataaatttt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattgggt	aaaagtga	catgttgtca	acctgggtgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaata	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttctact	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacgggttt	attgtgacgc	ttagcctggt	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgctgcg	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaataatg	ctaataaaga	tcacggcaa	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcattttttgc	cgtggctcggc	atgcagctct	3000
ttggtaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtgtt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcgatgtgt	catggtgatt	ggaaacctag	tggctctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgacg	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360
aattttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagcttta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaatttaaac	acggaagact	3660
ttagtagtga	atcggatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttgtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaatcaa	tgtggaagaa	ggcagaggaa	aacaatgggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtggtgctct	ggcatttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaatatgc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tatttcacca	atgcctgggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attgggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttggagcca	4200
tcaaactctct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgaggg	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatattctgg	ctaattttca	gcacatggg	cgtaaatttg	tttgctggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attgggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatggctct	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atgggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctattttac	tggagagtgt	gtactgaaac	5040

tcattctctct	acgccattat	tatttttacca	ttggatggaa	tattttttgat	tttgtggttg	5100
tcattctctc	cattgtaggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160
ctaccctgtt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttcct	gcgttgttta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcattctacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatggt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgaactgt	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttcct	ggttgtggtg	aacatgtaca	tcgcggtcat	cctggagAAC	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgaggttt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcattggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaaccaa	caaactccag	ctcattgcca	5820
tggatttgcc	catggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaaggtct	cctatcagcc	aatcactact	actttaaaac	6000
gaaaacaaga	ggaagtatct	gctgtcatta	ttcagcgtgc	ttacagaggc	caccttttaa	6060
agcgaactgt	aaaacaagct	tccttttacgt	acaataaaaa	caaaatcaaa	gggtggggcta	6120
atcttcttat	aaaagaagac	atgataattg	acagaataaa	tgaaaactct	attacagaaa	6180
aaactgatct	gaccatgtcc	actgcagctt	gtccaccttc	ctatgaccgg	gtgacaaagc	6240
caattgtgga	aaaacatgag	caagaaggca	aagatgaaaa	agccaaaggg	aaataaatga	6300
aaataaataa	aaataattgg	gtgacaaatt	gtttacagcc	tgtgaaggtg	atgtattttt	6360
atcaacagga	ctccttttagg	aggteaagtc	caaactgact	gtttttacac	aaatctcctt	6420
aaggtcagtg	cctacaataa	gacagtgacc	ccttgctcagc	aaactgtgac	tctgtgtaaa	6480
ggggagatga	ccttgacagg	aggttactgt	tctcactacc	agctgacact	gctgaagata	6540
agatgcacaa	tggctagtca	gactgtaggg	accagtttca	aggggtgcaa	acctgtgatt	6600
ttgggggttg	ttaacatgaa	acacttttagt	gtagtaattg	tatccactgt	ttgcatttca	6660
actgccacat	ttgtcacatt	tttatggaat	ctgttagtg	attcatcttt	ttgttaatcc	6720
atgtgtttat	tatatgtgac	tattttttgta	aacgaagttt	ctgttgagaa	ataggctaag	6780
gacctctata	acaggtatgc	cacctggggg	gtatggcaac	cacatggccc	tcccagctac	6840
acaaagtcgt	ggtttgcatg	agggcagctc	gcacttagag	atcatgcatg	agaaaaagtc	6900
acaagaaaaa	caaattctta	aatttcacca	tattttctggg	aggggttaatt	gggtgataag	6960
tggaggtgct	ttgttgatct	tgttttgcca	aatccagccc	ctagaccaag	tagattattt	7020
gtgggtaggg	cagtaaatct	tagcaggtgc	aaacttcatt	caaagtgttg	gagtcataaa	7080
tgttatgttt	ctttttgttg	tattaaaaaa	aaaacctgaa	tagtgaatat	tgccctcac	7140
cctccaccgc	cagaagactg	aattgaccaa	aattactctt	tataaatttc	tgctttttcc	7200
tgcaactttgt	ttagccatct	ttgggctctc	agcaaggttg	acactgtata	tgtaaatgaa	7260
atgctattta	ttatgtaaat	agtcattttta	ccctgtgggtg	cacgtttgag	caaacaaata	7320
atgacctaag	cacagtattt	attgcatcaa	atatgtacca	caagaaatgt	agagtgcag	7380
ctttacacag	gtaataaaat	gtattctgta	ccattttatag	atagtttgga	tgctatcaat	7440
gcatgtttat	attaccatgc	tgctgtatct	ggtttctctc	actgctcaga	atctcattta	7500
tgagaaacca	tatgtcagtg	gtaaagtcaa	ggaaattggt	caacagatct	cattttattta	7560
agtcattaag	caatagtttg	cagcacttta	acagcttttt	ggttattttt	acatttttaag	7620
tggataacat	atggtatata	gccagactgt	acagacatgt	ttaaaaaaac	acactgctta	7680
acctattaaa	tatgtgttta	gaattttata	agcaaataa	aatactgtaa	aaagtcactt	7740
tattttattt	ttcagcatta	tgtacataaa	tatgaagagg	aaattatctt	cagggtgata	7800
tcacaatcac	ttttcttact	ttctgtccat	agtacttttt	catgaaagaa	atttgctaaa	7860
taagacatga	aaacaagact	gggtagttgt	agattttctgc	tttttaaatt	acatttgcta	7920
attttagatt	atttcacaat	tttaaggagc	aaaatagggt	cacgattcat	atccaaatta	7980
tgctttgcaa	ttggaaaagg	gtttaaaatt	ttattttatat	ttctggtagt	acctgtacta	8040
actgaattga	aggtagtgct	tatgttattt	ttgttctttt	tttctgactt	cggtttatgt	8100
tttcattttct	ttggagtaat	gctgctctag	attgttctaa	atagaatgtg	ggcttcataa	8160
tttttttttc	cacaaaaaca	gagtagtcaa	cttatatagt	caattacatc	aggacatttt	8220
gtgtttctta	cagaagcaaa	ccataggctc	ctcttttctt	taaaactact	tagataaact	8280
gtattcgtga	actgcatgct	ggaaaatgct	actattatgc	taaataatgc	taaccaacat	8340
ttaaaatgtg	caaaactaat	aaagattaca	ttttttattt	t		8381

<210> 12

<211> 2009

<212> PRT

<213> Homo sapiens

<400> 12

Met	Glu	Gln	Thr	Val	Leu	Val	Pro	Pro	Gly	Pro	Asp	Ser	Phe	Asn	Phe
1				5					10					15	
Phe	Thr	Arg	Glu	Ser	Leu	Ala	Ala	Ile	Glu	Arg	Arg	Ile	Ala	Glu	Glu
			20					25					30		
Lys	Ala	Lys	Asn	Pro	Lys	Pro	Asp	Lys	Lys	Asp	Asp	Asp	Glu	Asn	Gly
	35						40					45			
Pro	Lys	Pro	Asn	Ser	Asp	Leu	Glu	Ala	Gly	Lys	Asn	Leu	Pro	Phe	Ile
	50					55					60				
Tyr	Gly	Asp	Ile	Pro	Pro	Glu	Met	Val	Ser	Glu	Pro	Leu	Glu	Asp	Leu
65					70					75					80
Asp	Pro	Tyr	Tyr	Ile	Asn	Lys	Lys	Thr	Phe	Ile	Val	Leu	Asn	Lys	Leu
				85					90					95	
Lys	Ala	Ile	Phe	Arg	Phe	Ser	Ala	Thr	Ser	Ala	Leu	Tyr	Ile	Leu	Thr
			100					105					110		
Pro	Phe	Asn	Pro	Leu	Arg	Lys	Ile	Ala	Ile	Lys	Ile	Leu	Val	His	Ser
		115					120					125			
Leu	Phe	Ser	Met	Leu	Ile	Met	Cys	Thr	Ile	Leu	Thr	Asn	Cys	Val	Phe
	130					135					140				
Met	Thr	Met	Ser	Asn	Pro	Pro	Asp	Trp	Thr	Lys	Asn	Val	Glu	Tyr	Thr
145					150					155					160
Phe	Thr	Gly	Ile	Tyr	Thr	Phe	Glu	Ser	Leu	Ile	Lys	Ile	Ile	Ala	Arg
			165						170					175	
Gly	Phe	Cys	Leu	Glu	Asp	Phe	Thr	Phe	Leu	Arg	Asp	Pro	Trp	Asn	Trp
			180					185					190		
Leu	Asp	Phe	Thr	Val	Ile	Thr	Phe	Ala	Tyr	Val	Thr	Glu	Phe	Val	Asp
	195						200					205			
Leu	Gly	Asn	Val	Ser	Ala	Leu	Arg	Thr	Phe	Arg	Val	Leu	Arg	Ala	Leu
	210					215					220				
Lys	Thr	Ile	Ser	Val	Ile	Pro	Gly	Leu	Lys	Thr	Ile	Val	Gly	Ala	Leu
225					230					235					240
Ile	Gln	Ser	Val	Lys	Lys	Leu	Ser	Asp	Val	Met	Ile	Leu	Thr	Val	Phe
			245						250					255	
Cys	Leu	Ser	Val	Phe	Ala	Leu	Ile	Gly	Leu	Gln	Leu	Phe	Met	Gly	Asn
			260					265					270		
Leu	Arg	Asn	Lys	Cys	Ile	Gln	Trp	Pro	Pro	Thr	Asn	Ala	Ser	Leu	Glu
		275					280					285			
Glu	His	Ser	Ile	Glu	Lys	Asn	Ile	Thr	Val	Asn	Tyr	Asn	Gly	Thr	Leu
	290					295					300				
Ile	Asn	Glu	Thr	Val	Phe	Glu	Phe	Asp	Trp	Lys	Ser	Tyr	Ile	Gln	Asp
305					310					315					320
Ser	Arg	Tyr	His	Tyr	Phe	Leu	Glu	Gly	Phe	Leu	Asp	Ala	Leu	Leu	Cys
			325						330					335	
Gly	Asn	Ser	Ser	Asp	Ala	Gly	Gln	Cys	Pro	Glu	Gly	Tyr	Met	Cys	Val
			340					345					350		
Lys	Ala	Gly	Arg	Asn	Pro	Asn	Tyr	Gly	Tyr	Thr	Ser	Phe	Asp	Thr	Phe
		355					360					365			
Ser	Trp	Ala	Phe	Leu	Ser	Leu	Phe	Arg	Leu	Met	Thr	Gln	Asp	Phe	Trp
	370					375					380				
Glu	Asn	Leu	Tyr	Gln	Leu	Thr	Leu	Arg	Ala	Ala	Gly	Lys	Thr	Tyr	Met
385					390					395					400
Ile	Phe	Phe	Val	Leu	Val	Ile	Phe	Leu	Gly	Ser	Phe	Tyr	Leu	Ile	Asn
			405						410					415	
Leu	Ile	Leu	Ala	Val	Val	Ala	Met	Ala	Tyr	Glu	Glu	Gln	Asn	Gln	Ala
			420					425					430		

Thr	Leu	Glu	Glu	Ala	Glu	Gln	Lys	Glu	Ala	Glu	Phe	Gln	Gln	Met	Ile
	435						440				445				
Glu	Gln	Leu	Lys	Lys	Gln	Gln	Glu	Ala	Ala	Gln	Gln	Ala	Ala	Thr	Ala
	450					455					460				
Thr	Ala	Ser	Glu	His	Ser	Arg	Glu	Pro	Ser	Ala	Ala	Gly	Arg	Leu	Ser
465					470					475					480
Asp	Ser	Ser	Ser	Glu	Ala	Ser	Lys	Leu	Ser	Ser	Lys	Ser	Ala	Lys	Glu
				485					490					495	
Arg	Arg	Asn	Arg	Arg	Lys	Lys	Arg	Lys	Gln	Lys	Glu	Gln	Ser	Gly	Gly
		500						505					510		
Glu	Glu	Lys	Asp	Glu	Asp	Glu	Phe	Gln	Lys	Ser	Glu	Ser	Glu	Asp	Ser
		515					520						525		
Ile	Arg	Arg	Lys	Gly	Phe	Arg	Phe	Ser	Ile	Glu	Gly	Asn	Arg	Leu	Thr
	530					535					540				
Tyr	Glu	Lys	Arg	Tyr	Ser	Ser	Pro	His	Gln	Ser	Leu	Leu	Ser	Ile	Arg
545					550					555					560
Gly	Ser	Leu	Phe	Ser	Pro	Arg	Arg	Asn	Ser	Arg	Thr	Ser	Leu	Phe	Ser
				565				570						575	
Phe	Arg	Gly	Arg	Ala	Lys	Asp	Val	Gly	Ser	Glu	Asn	Asp	Phe	Ala	Asp
			580					585					590		
Asp	Glu	His	Ser	Thr	Phe	Glu	Asp	Asn	Glu	Ser	Arg	Arg	Asp	Ser	Leu
	595						600					605			
Phe	Val	Pro	Arg	Arg	His	Gly	Glu	Arg	Arg	Asn	Ser	Asn	Leu	Ser	Gln
	610					615						620			
Thr	Ser	Arg	Ser	Ser	Arg	Met	Leu	Ala	Val	Phe	Pro	Ala	Asn	Gly	Lys
625					630					635					640
Met	His	Ser	Thr	Val	Asp	Cys	Asn	Gly	Val	Val	Ser	Leu	Val	Gly	Gly
				645				650						655	
Pro	Ser	Val	Pro	Thr	Ser	Pro	Val	Gly	Gln	Leu	Leu	Pro	Glu	Val	Ile
			660					665					670		
Ile	Asp	Lys	Pro	Ala	Thr	Asp	Asp	Asn	Gly	Thr	Thr	Thr	Glu	Thr	Glu
	675						680					685			
Met	Arg	Lys	Arg	Arg	Ser	Ser	Ser	Phe	His	Val	Ser	Met	Asp	Phe	Leu
	690					695					700				
Glu	Asp	Pro	Ser	Gln	Arg	Gln	Arg	Ala	Met	Ser	Ile	Ala	Ser	Ile	Leu
705					710					715					720
Thr	Asn	Thr	Val	Glu	Glu	Leu	Glu	Glu	Ser	Arg	Gln	Lys	Cys	Pro	Pro
			725					730						735	
Cys	Trp	Tyr	Lys	Phe	Ser	Asn	Ile	Phe	Leu	Ile	Trp	Asp	Cys	Ser	Pro
		740						745					750		
Tyr	Trp	Leu	Lys	Val	Lys	His	Val	Val	Asn	Leu	Val	Val	Met	Asp	Pro
	755						760						765		
Phe	Val	Asp	Leu	Ala	Ile	Thr	Ile	Cys	Ile	Val	Leu	Asn	Thr	Leu	Phe
	770					775					780				
Met	Ala	Met	Glu	His	Tyr	Pro	Met	Thr	Asp	His	Phe	Asn	Asn	Val	Leu
785					790					795					800
Thr	Val	Gly	Asn	Leu	Val	Phe	Thr	Gly	Ile	Phe	Thr	Ala	Glu	Met	Phe
			805					810						815	
Leu	Lys	Ile	Ile	Ala	Met	Asp	Pro	Tyr	Tyr	Tyr	Phe	Gln	Glu	Gly	Trp
			820					825					830		
Asn	Ile	Phe	Asp	Gly	Phe	Ile	Val	Thr	Leu	Ser	Leu	Val	Glu	Leu	Gly
	835						840					845			
Leu	Ala	Asn	Val	Glu	Gly	Leu	Ser	Val	Leu	Arg	Ser	Phe	Arg	Leu	Leu
	850					855					860				
Arg	Val	Phe	Lys	Leu	Ala	Lys	Ser	Trp	Pro	Thr	Leu	Asn	Met	Leu	Ile
865					870					875					880
Lys	Ile	Ile	Gly	Asn	Ser	Val	Gly	Ala	Leu	Gly	Asn	Leu	Thr	Leu	Val
			885					890						895	

Leu	Ala	Ile	Ile	Val	Phe	Ile	Phe	Ala	Val	Val	Gly	Met	Gln	Leu	Phe
			900					905					910		
Gly	Lys	Ser	Tyr	Lys	Asp	Cys	Val	Cys	Lys	Ile	Ala	Ser	Asp	Cys	Gln
		915					920					925			
Leu	Pro	Arg	Trp	His	Met	Asn	Asp	Phe	Phe	His	Ser	Phe	Leu	Ile	Val
	930					935					940				
Phe	Arg	Val	Leu	Cys	Gly	Glu	Trp	Ile	Glu	Thr	Met	Trp	Asp	Cys	Met
945					950					955					960
Glu	Val	Ala	Gly	Gln	Ala	Met	Cys	Leu	Thr	Val	Phe	Met	Met	Val	Met
			965						970					975	
Val	Ile	Gly	Asn	Leu	Val	Val	Leu	Asn	Leu	Phe	Leu	Ala	Leu	Leu	Leu
			980					985					990		
Ser	Ser	Phe	Ser	Ala	Asp	Asn	Leu	Ala	Ala	Thr	Asp	Asp	Asp	Asn	Glu
		995					1000					1005			
Met	Asn	Asn	Leu	Gln	Ile	Ala	Val	Asp	Arg	Met	His	Lys	Gly	Val	
	1010					1015					1020				
Ala	Tyr	Val	Lys	Arg	Lys	Ile	Tyr	Glu	Phe	Ile	Gln	Gln	Ser	Phe	
	1025					1030					1035				
Ile	Arg	Lys	Gln	Lys	Ile	Leu	Asp	Glu	Ile	Lys	Pro	Leu	Asp	Asp	
	1040					1045					1050				
Leu	Asn	Asn	Lys	Lys	Asp	Ser	Cys	Met	Ser	Asn	His	Thr	Thr	Glu	
	1055					1060					1065				
Ile	Gly	Lys	Asp	Leu	Asp	Tyr	Leu	Lys	Asp	Val	Asn	Gly	Thr	Thr	
	1070					1075					1080				
Ser	Gly	Ile	Gly	Thr	Gly	Ser	Ser	Val	Glu	Lys	Tyr	Ile	Ile	Asp	
	1085					1090					1095				
Glu	Ser	Asp	Tyr	Met	Ser	Phe	Ile	Asn	Asn	Pro	Ser	Leu	Thr	Val	
	1100					1105					1110				
Thr	Val	Pro	Ile	Ala	Val	Gly	Glu	Ser	Asp	Phe	Glu	Asn	Leu	Asn	
	1115					1120					1125				
Thr	Glu	Asp	Phe	Ser	Ser	Glu	Ser	Asp	Leu	Glu	Glu	Ser	Lys	Glu	
	1130					1135					1140				
Lys	Leu	Asn	Glu	Ser	Ser	Ser	Ser	Ser	Glu	Gly	Ser	Thr	Val	Asp	
	1145					1150					1155				
Ile	Gly	Ala	Pro	Val	Glu	Glu	Gln	Pro	Val	Val	Glu	Pro	Glu	Glu	
	1160					1165					1170				
Thr	Leu	Glu	Pro	Glu	Ala	Cys	Phe	Thr	Glu	Gly	Cys	Val	Gln	Arg	
	1175					1180					1185				
Phe	Lys	Cys	Cys	Gln	Ile	Asn	Val	Glu	Glu	Gly	Arg	Gly	Lys	Gln	
	1190					1195					1200				
Trp	Trp	Asn	Leu	Arg	Arg	Thr	Cys	Phe	Arg	Ile	Val	Glu	His	Asn	
	1205					1210					1215				
Trp	Phe	Glu	Thr	Phe	Ile	Val	Phe	Met	Ile	Leu	Leu	Ser	Ser	Gly	
	1220					1225					1230				
Ala	Leu	Ala													

Ala	Leu	Leu	Gly	Ala	Ile	Pro	Ser	Ile	Met	Asn	Val	Leu	Leu	Val
1340						1345					1350			
Cys	Leu	Ile	Phe	Trp	Leu	Ile	Phe	Ser	Ile	Met	Gly	Val	Asn	Leu
1355						1360					1365			
Phe	Ala	Gly	Lys	Phe	Tyr	His	Cys	Ile	Asn	Thr	Thr	Thr	Gly	Asp
1370						1375					1380			
Arg	Phe	Asp	Ile	Glu	Asp	Val	Asn	Asn	His	Thr	Asp	Cys	Leu	Lys
1385						1390					1395			
Leu	Ile	Glu	Arg	Asn	Glu	Thr	Ala	Arg	Trp	Lys	Asn	Val	Lys	Val
1400						1405					1410			
Asn	Phe	Asp	Asn	Val	Gly	Phe	Gly	Tyr	Leu	Ser	Leu	Leu	Gln	Val
1415						1420					1425			
Ala	Thr	Phe	Lys	Gly	Trp	Met	Asp	Ile	Met	Tyr	Ala	Ala	Val	Asp
1430						1435					1440			
Ser	Arg	Asn	Val	Glu	Leu	Gln	Pro	Lys	Tyr	Glu	Lys	Ser	Leu	Tyr
1445						1450					1455			
Met	Tyr	Leu	Tyr	Phe	Val	Ile	Phe	Ile	Ile	Phe	Gly	Ser	Phe	Phe
1460						1465					1470			
Thr	Leu	Asn	Leu	Phe	Ile	Gly	Val	Ile	Ile	Asp	Asn	Phe	Asn	Gln
1475						1480					1485			
Gln	Lys	Lys	Lys	Phe	Gly	Gly	Gln	Asp	Ile	Phe	Met	Thr	Glu	Glu
1490						1495					1500			
Gln	Lys	Lys	Tyr	Tyr	Asn	Ala	Met	Lys	Lys	Leu	Gly	Ser	Lys	Lys
1505						1510					1515			
Pro	Gln	Lys	Pro	Ile	Pro	Arg	Pro	Gly	Asn	Lys	Phe	Gln	Gly	Met
1520						1525					1530			
Val	Phe	Asp	Phe	Val	Thr	Arg	Gln	Val	Phe	Asp	Ile	Ser	Ile	Met
1535						1540					1545			
Ile	Leu	Ile	Cys	Leu	Asn	Met	Val	Thr	Met	Met	Val	Glu	Thr	Asp
1550						1555					1560			
Asp	Gln	Ser	Glu	Tyr	Val	Thr	Thr	Ile	Leu	Ser	Arg	Ile	Asn	Leu
1565						1570					1575			
Val	Phe	Ile	Val	Leu	Phe	Thr	Gly	Glu	Cys	Val	Leu	Lys	Leu	Ile
1580						1585					1590			
Ser	Leu	Arg	His	Tyr	Tyr	Phe	Thr	Ile	Gly	Trp	Asn	Ile	Phe	Asp
1595						1600					1605			
Phe	Val	Val	Val	Ile	Leu	Ser	Ile	Val	Gly	Met	Phe	Leu	Ala	Glu
1610						1615					1620			
Leu	Ile	Glu	Lys	Tyr	Phe	Val	Ser	Pro	Thr	Leu	Phe	Arg	Val	Ile
1625						1630					1635			
Arg	Leu	Ala	Arg	Ile	Gly	Arg	Ile	Leu	Arg	Leu	Ile	Lys	Gly	Ala
1640						1645					1650			
Lys	Gly	Ile	Arg	Thr	Leu	Leu	Phe	Ala	Leu	Met	Met	Ser	Leu	Pro
1655						1660					1665			
Ala	Leu	Phe	Asn	Ile	Gly	Leu	Leu	Leu	Phe	Leu	Val	Met	Phe	Ile
1670						1675					1680			
Tyr	Ala	Ile	Phe	Gly	Met	Ser	Asn	Phe	Ala	Tyr	Val	Lys	Arg	Glu
1685						1690					1695			
Val	Gly	Ile	Asp	Asp	Met	Phe	Asn	Phe	Glu	Thr	Phe	Gly	Asn	Ser
1700						1705					1710			
Met	Ile	Cys	Leu	Phe	Gln	Ile	Thr	Thr	Ser	Ala	Gly	Trp	Asp	Gly
1715						1720					1725			
Leu	Leu	Ala	Pro	Ile	Leu	Asn	Ser	Lys	Pro	Pro	Asp	Cys	Asp	Pro
1730						1735					1740			
Asn	Lys	Val	Asn	Pro	Gly	Ser	Ser	Val	Lys	Gly	Asp	Cys	Gly	Asn
1745						1750					1755			
Pro	Ser	Val	Gly	Ile	Phe	Phe	Phe	Val	Ser	Tyr	Ile	Ile	Ile	Ser
1760						1765					1770			

Phe	Leu	Val	Val	Val	Asn	Met	Tyr	Ile	Ala	Val	Ile	Leu	Glu	Asn
1775						1780					1785			
Phe	Ser	Val	Ala	Thr	Glu	Glu	Ser	Ala	Glu	Pro	Leu	Ser	Glu	Asp
1790						1795					1800			
Asp	Phe	Glu	Met	Phe	Tyr	Glu	Val	Trp	Glu	Lys	Phe	Asp	Pro	Asp
1805						1810					1815			
Ala	Thr	Gln	Phe	Met	Glu	Phe	Glu	Lys	Leu	Ser	Gln	Phe	Ala	Ala
1820						1825					1830			
Ala	Leu	Glu	Pro	Pro	Leu	Asn	Leu	Pro	Gln	Pro	Asn	Lys	Leu	Gln
1835						1840					1845			
Leu	Ile	Ala	Met	Asp	Leu	Pro	Met	Val	Ser	Gly	Asp	Arg	Ile	His
1850						1855					1860			
Cys	Leu	Asp	Ile	Leu	Phe	Ala	Phe	Thr	Lys	Arg	Val	Leu	Gly	Glu
1865						1870					1875			
Ser	Gly	Glu	Met	Asp	Ala	Leu	Arg	Ile	Gln	Met	Glu	Glu	Arg	Phe
1880						1885					1890			
Met	Ala	Ser	Asn	Pro	Ser	Lys	Val	Ser	Tyr	Gln	Pro	Ile	Thr	Thr
1895						1900					1905			
Thr	Leu	Lys	Arg	Lys	Gln	Glu	Glu	Val	Ser	Ala	Val	Ile	Ile	Gln
1910						1915					1920			
Arg	Ala	Tyr	Arg	Gly	His	Leu	Leu	Lys	Arg	Thr	Val	Lys	Gln	Ala
1925						1930					1935			
Ser	Phe	Thr	Tyr	Asn	Lys	Asn	Lys	Ile	Lys	Gly	Gly	Ala	Asn	Leu
1940						1945					1950			
Leu	Ile	Lys	Glu	Asp	Met	Ile	Ile	Asp	Arg	Ile	Asn	Glu	Asn	Ser
1955						1960					1965			
Ile	Thr	Glu	Lys	Thr	Asp	Leu	Thr	Met	Ser	Thr	Ala	Ala	Cys	Pro
1970						1975					1980			
Pro	Ser	Tyr	Asp	Arg	Val	Thr	Lys	Pro	Ile	Val	Glu	Lys	His	Glu
1985						1990					1995			
Gln	Glu	Gly	Lys	Asp	Glu	Lys	Ala	Lys	Gly	Lys				
2000						2005								

<210> 13
 <211> 27
 <212> DNA
 <213> Homo sapiens

<400> 13
 agatgaccag agtgaatatg tgactac

27

<210> 14
 <211> 24
 <212> DNA
 <213> Homo sapiens

<400> 14
 ccaatggtaa aataataatg gcgt

24

<210> 15
 <211> 20
 <212> DNA
 <213> Homo sapiens

<400> 15
 taccatagag tgaggcgagg

20

<210> 16
<211> 20
<212> DNA
<213> Homo sapiens

<400> 16
atggacttcc tgctctgccc 20

<210> 17
<211> 22
<212> DNA
<213> Homo sapiens

<400> 17
cctctagctc atgtttcatg ac 22

<210> 18
<211> 20
<212> DNA
<213> Homo sapiens

<400> 18
tgtagtaggc aattagcagc 20

<210> 19
<211> 26
<212> DNA
<213> Homo sapiens

<400> 19
ctaattaaga agagatccag tgacag 26

<210> 20
<211> 27
<212> DNA
<213> Homo sapiens

<400> 20
gctataaagt gcttacagat catgtac 27

<210> 21
<211> 24
<212> DNA
<213> Homo sapiens

<400> 21
ccctgaattt tggctaagct gcag 24

<210> 22
<211> 27
<212> DNA
<213> Homo sapiens

<400> 22
ctacattaag acacagtttc aaaatcc 27

<210> 23
<211> 21
<212> DNA
<213> Homo sapiens

<400> 23
gggctacgtt tcatttgtat g 21

<210> 24
<211> 27
<212> DNA
<213> Homo sapiens

<400> 24
gcaacctatt cttaaagcat aagactg 27

<210> 25
<211> 20
<212> DNA
<213> Homo sapiens

<400> 25
aggctctttg tacctacagc 20

<210> 26
<211> 20
<212> DNA
<213> Homo sapiens

<400> 26
catgtagggc ccgtctcatt 20

<210> 27
<211> 23
<212> DNA
<213> Homo sapiens

<400> 27
cacacgtgtt aagtcttcat agt 23

<210> 28
<211> 21
<212> DNA
<213> Homo sapiens

<400> 28
agccccctcaa gtatttatcc t 21

<210> 29
<211> 21

<212> DNA
<213> Homo sapiens

<400> 29
gaacctgacc ttcctgttct c 21

<210> 30
<211> 22
<212> DNA
<213> Homo sapiens

<400> 30
gttggctggt atcttcagtt tc 22

<210> 31
<211> 23
<212> DNA
<213> Homo sapiens

<400> 31
gactaggcaa tatcatagca tag 23

<210> 32
<211> 23
<212> DNA
<213> Homo sapiens

<400> 32
ctttctacta tattatcatc cgg 23

<210> 33
<211> 20
<212> DNA
<213> Homo sapiens

<400> 33
ttgaaagttg aagccaccac 20

<210> 34
<211> 20
<212> DNA
<213> Homo sapiens

<400> 34
ccacctgctc ttaggtactc 20

<210> 35
<211> 21
<212> DNA
<213> Homo sapiens

<400> 35
gccatgcaaa tacttcagcc c 21

<210> 36
<211> 23
<212> DNA
<213> Homo sapiens

<400> 36
cacaacagtg gttgattcag ttg

23

<210> 37
<211> 23
<212> DNA
<213> Homo sapiens

<400> 37
tgaatgctga aatctccttc tac

23

<210> 38
<211> 21
<212> DNA
<213> Homo sapiens

<400> 38
ctcaggttgc tggtgcgtct c

21

<210> 39
<211> 21
<212> DNA
<213> Homo sapiens

<400> 39
gataacgaga gccgtagaga t

21

<210> 40
<211> 20
<212> DNA
<213> Homo sapiens

<400> 40
tctgtagaaa cactggctgg

20

<210> 41
<211> 21
<212> DNA
<213> Homo sapiens

<400> 41
catgaaattc actgtgtcac c

21

<210> 42
<211> 21
<212> DNA
<213> Homo sapiens

<400> 42
cagctcttga attagactgt c 21

<210> 43
<211> 20
<212> DNA
<213> Homo sapiens

<400> 43
atccttggga ggtttagagt 20

<210> 44
<211> 21
<212> DNA
<213> Homo sapiens

<400> 44
catcacaacc aggttgacaa c 21

<210> 45
<211> 21
<212> DNA
<213> Homo sapiens

<400> 45
ctgggactgt tctccatatt g 21

<210> 46
<211> 20
<212> DNA
<213> Homo sapiens

<400> 46
gcatgaagga tggttgaaag 20

<210> 47
<211> 23
<212> DNA
<213> Homo sapiens

<400> 47
cattgtggga aaatagcata agc 23

<210> 48
<211> 20
<212> DNA
<213> Homo sapiens

<400> 48
gctatgcaga accctgattg 20

<210> 49
<211> 20

<212> DNA
<213> Homo sapiens

<400> 49
tgagacgggtt agggcagatc 20

<210> 50
<211> 21
<212> DNA
<213> Homo sapiens

<400> 50
agaagtcatt catgtgccag c 21

<210> 51
<211> 21
<212> DNA
<213> Homo sapiens

<400> 51
ctgcaagatc gccagtgatt g 21

<210> 52
<211> 20
<212> DNA
<213> Homo sapiens

<400> 52
acatgtgcac aatgtgcagg 20

<210> 53
<211> 22
<212> DNA
<213> Homo sapiens

<400> 53
gtggtgtttc cttctcatca ag 22

<210> 54
<211> 22
<212> DNA
<213> Homo sapiens

<400> 54
tctgctgtat gattggacat ac 22

<210> 55
<211> 22
<212> DNA
<213> Homo sapiens

<400> 55
caacagtcct tcattaggaa ac 22

<210> 56
<211> 22
<212> DNA
<213> Homo sapiens

<400> 56
accttccac acctatagaa tc 22

<210> 57
<211> 21
<212> DNA
<213> Homo sapiens

<400> 57
cttggcaggc aacttattac c 21

<210> 58
<211> 22
<212> DNA
<213> Homo sapiens

<400> 58
caagctgcac tccaaatgaa ag 22

<210> 59
<211> 24
<212> DNA
<213> Homo sapiens

<400> 59
tggaagcaga gacactttat ctac 24

<210> 60
<211> 24
<212> DNA
<213> Homo sapiens

<400> 60
gtgctgtatc accttttctt aatc 24

<210> 61
<211> 24
<212> DNA
<213> Homo sapiens

<400> 61
cctattccaa tgaaatgtca tatg 24

<210> 62
<211> 21
<212> DNA
<213> Homo sapiens

<400> 62
caagctacct tgaacagaga c 21

<210> 63
<211> 24
<212> DNA
<213> Homo sapiens

<400> 63
ctacacattg aatgatgatt ctgt 24

<210> 64
<211> 24
<212> DNA
<213> Homo sapiens

<400> 64
gctatataca atacttcagg ttct 24

<210> 65
<211> 21
<212> DNA
<213> Homo sapiens

<400> 65
accagagatt actaggggaa t 21

<210> 66
<211> 21
<212> DNA
<213> Homo sapiens

<400> 66
ccatcgagca gtctcatttc t 21

<210> 67
<211> 21
<212> DNA
<213> Homo sapiens

<400> 67
acaactggtg acaggtttga c 21

<210> 68
<211> 24
<212> DNA
<213> Homo sapiens

<400> 68
ctgggctcat aaacttgtag taac 24

<210> 69
<211> 21

<212> DNA
<213> Homo sapiens

<400> 69
actgtcttgg tccaaaatct g 21

<210> 70
<211> 24
<212> DNA
<213> Homo sapiens

<400> 70
ttcgattaat ttaccacct gatc 24

<210> 71
<211> 21
<212> DNA
<213> Homo sapiens

<400> 71
agcaccagtg acatttccaa c 21

<210> 72
<211> 21
<212> DNA
<213> Homo sapiens

<400> 72
ggcagagaaa acactccaag g 21

<210> 73
<211> 21
<212> DNA
<213> Homo sapiens

<400> 73
gacacagttt taaccagttt g 21

<210> 74
<211> 21
<212> DNA
<213> Homo sapiens

<400> 74
tgtgagacaa gcatgcaagt t 21

<210> 75
<211> 21
<212> DNA
<213> Homo sapiens

<400> 75
cagggccaat gactactttg c 21

<210> 76
<211> 25
<212> DNA
<213> Homo sapiens

<400> 76
ctgattgctg ggatgatctt gaatc

25

<210> 77
<211> 23
<212> DNA
<213> Homo sapiens

<400> 77
cgcatgattt cttcactggt tgg

23

<210> 78
<211> 21
<212> DNA
<213> Homo sapiens

<400> 78
gcgtagatga acatgactag g

21

<210> 79
<211> 21
<212> DNA
<213> Homo sapiens

<400> 79
tcctgcgttg tttaacatcg g

21

<210> 80
<211> 21
<212> DNA
<213> Homo sapiens

<400> 80
attccaacag atgggttccc a

21

<210> 81
<211> 21
<212> DNA
<213> Homo sapiens

<400> 81
tggaagctca gttaagggag a

21

<210> 82
<211> 21
<212> DNA
<213> Homo sapiens

<400> 82
agcgcagctg caaactgaga t 21

<210> 83
<211> 22
<212> DNA
<213> Homo sapiens

<400> 83
ccgatgcaac tcagttcatg ga 22

<210> 84
<211> 21
<212> DNA
<213> Homo sapiens

<400> 84
gtagtgattg gctgatagga g 21

<210> 85
<211> 24
<212> DNA
<213> Homo sapiens

<400> 85
agagcgattc atggcttcca atcc 24

<210> 86
<211> 26
<212> DNA
<213> Homo sapiens

<400> 86
tgccttcttg ctcatgtttt tccaca 26

<210> 87
<211> 22
<212> DNA
<213> Homo sapiens

<400> 87
cctatgaccg ggtgacaaag cc 22

<210> 88
<211> 22
<212> DNA
<213> Homo sapiens

<400> 88
tgctgacaag gggtcactgt ct 22

<210> 89
<211> 8381

<212> DNA

<213> Homo sapiens

<400> 89

atactgcaga	ggtctctggt	gcatgtgtgt	atgtgtgctg	ttgtgtgtgt	ttgtgtgtct	60
gtgtgttctg	ccccagtgag	actgcagccc	ttgtaaatac	tttgacacct	tttgcaagaa	120
ggaatctgaa	caattgcaac	tgaaggcaca	ttgttatcat	ctcgtctttg	ggtgatgctg	180
ttcctcactg	cagatggata	attttccttt	taatcaggaa	tttcatatgc	agaataaatg	240
gtaattaaaa	tgtgcaggat	gacaagatgg	agcaaacagt	gcttgtacca	ccaggacctg	300
acagcttcaa	cttcttcacc	agagaatctc	ttgctggctat	tgaaagacgc	attgcagaag	360
aaaaggcaaa	gaatcccaaa	ccagacaaaa	aagatgacga	cgaaaatggc	ccaaagccaa	420
atagtgactt	ggaagctgga	aagaaccttc	catttatatta	tggagacatt	cctccagaga	480
tggtgtcaga	gcccctggag	gacctggacc	cctactatat	caataagaaa	acttttatag	540
tattgaataa	attgaaggcc	atcttccggg	tcagtgccac	ctctgccctg	tacattttta	600
ctcccttcaa	tcctcttagg	aaaatagcta	ttaagatttt	ggtacattca	ttattcagca	660
tgctaattat	gtgcactatt	ttgacaaact	gtgtgtttat	gacaatgagt	aacctcctg	720
attggacaaa	gaatgtagaa	tacaccttca	caggaatata	tacttttgaa	tcacttataa	780
aaattattgc	aaggggattc	tgtttagaag	attttacttt	ccttcgggat	ccatggaact	840
ggctcgattt	cactgtcatt	acatttgcgt	acgtcacaga	gtttgtggac	ctgggcaatg	900
tctcggcatt	gagaacattc	agagttctcc	gagcattgaa	gacgatttca	gtcattccag	960
gcctgaaaac	cattgtggga	gccctgatcc	agtctgtgaa	gaagctctca	gatgtaatga	1020
tcctgactgt	gttctgtctg	agcgtatttg	ctctaattgg	gctgcagctg	ttcatgggca	1080
acctgaggaa	taaatgtata	caatggcctc	ccaccaatgc	ttccttggag	gaacatagta	1140
tagaaaagaa	tataactgtg	aattataatg	gtacacttat	aaatgaaact	gtctttgagt	1200
ttgactggaa	gtcatatatt	caagattcaa	gatatcatta	tttcctggag	ggttttttag	1260
atgcactact	atgtggaaat	agctctgatg	caggccaatg	tccagaggga	tatatgtgtg	1320
tgaaagctgg	tagaaatccc	aattatggct	acacaagctt	tgataccttc	agttgggctt	1380
ttttgtcctt	gtttcgacta	atgactcagg	acttctggga	aaatctttat	caactgacat	1440
tacgtgctgc	tgggaaaacg	tacatgatat	tttttgtatt	ggtcattttc	ttgggctcat	1500
tctacctaat	aaatttgatc	ctggctgtgg	tggccatggc	ctacgaggaa	cagaatcagg	1560
ccaccttgga	agaagcagaa	cagaaagagg	ccgaatttca	gcagatgatt	gaacagctta	1620
aaaagcaaca	ggaggcagct	cagcaggcag	caacggcaac	tgcttcagaa	cattccagag	1680
agcccagtgc	agcaggcagg	ctctcagaca	gctcatctga	agcctctaag	ttgagttcca	1740
agagtgctaa	ggaaagaaga	aatcggagga	agaaaagaaa	acagaaagag	cagtctggtg	1800
gggaagagaa	agatgaggat	gaattccaaa	aatctgaatc	tgaggacagc	atcaggagga	1860
aaggttttctg	cttctccatt	gaagggaacc	gattgacata	tgaaaagagg	tactcctccc	1920
cacaccagtc	tttgttgagc	atccgtggct	ccctattttc	accaaggcga	aatagcagaa	1980
caagcctttt	cagctttaga	gggcgagcaa	aggatgtggg	atctgagaac	gacttcgcag	2040
atgatgagca	cagcaccttt	gaggataacg	agagccgtag	agattccttg	tttgtgcccc	2100
gacgacacgg	agagagacgc	aacagcaacc	tgagtcagac	cagtaggtca	tcccggatgc	2160
tggcagtgtt	tccagcgaat	gggaagatgc	acagcactgt	ggattgcaat	ggtgtgggtt	2220
ccttggttgg	tggaccttca	gttcctacat	cgctgttggg	acagcttctg	ccagaggtga	2280
taatagataa	gccagctact	gatgacaatg	gaacaaccac	tgaaactgaa	atgagaaaga	2340
gaaggtcaag	ttctttccac	gtttccatgg	actttctaga	agatccttcc	caaaggcaac	2400
gagcaatgag	tatagccagc	attctaacia	atacagtaga	agaacttgaa	gaatccaggc	2460
agaaatgccc	accctgttgg	tataaatttt	ccaacatatt	cttaatctgg	gactgttctc	2520
catattgggt	aaaagtgaag	catgttgtca	acctgggtgt	gatggacca	tttgttgacc	2580
tggccatcac	catctgtatt	gtcttaaaata	ctcttttcat	ggccatggag	cactatccaa	2640
tgacggacca	tttcaataat	gtgcttacag	taggaaactt	ggttttctact	gggatcttta	2700
cagcagaaat	gtttctgaaa	attattgcca	tggatcctta	ctattatttc	caagaaggct	2760
ggaatatctt	tgacggtttt	attgtgacgc	ttagcctggg	agaacttgga	ctcgccaatg	2820
tgggaaggatt	atctgttctc	cgttcatttc	gattgtctgc	agttttcaag	ttggcaaaat	2880
cttggccaac	gttaaatatg	ctaataaaga	tcatcgga	ttccgtgggg	gctctgggaa	2940
atttaaccct	cgtcttggcc	atcatcgtct	tcatttttgc	cgtggctggc	atgcagctct	3000
ttggtaaaag	ctacaaagat	tgtgtctgca	agatcgccag	tgattgtcaa	ctcccacgct	3060
ggcacatgaa	tgacttcttc	cactccttcc	tgattgtgtt	ccgcgtgctg	tgtggggagt	3120
ggatagagac	catgtgggac	tgtatggagg	ttgctgggtca	agccatgtgc	cttactgtct	3180
tcatgatggg	catggtgatt	ggaaacctag	tggctcctgaa	tctctttctg	gccttgcttc	3240
tgagctcatt	tagtgcagac	aaccttgacg	ccactgatga	tgataatgaa	atgaataatc	3300
tccaaattgc	tgtggatagg	atgcacaaag	gagtagctta	tgtgaaaaga	aaaatatatg	3360

aattttattca	acagtccttc	attaggaaac	aaaagatttt	agatgaaatt	aaaccacttg	3420
atgatctaaa	caacaagaaa	gacagttgta	tgtccaatca	tacaacagaa	attgggaaag	3480
atcttgacta	tcttaaagat	gtaaatggaa	ctacaagtgg	tataggaact	ggcagcagtg	3540
ttgaaaaata	cattattgat	gaaagtgatt	acatgtcatt	cataaacaac	cccagtctta	3600
ctgtgactgt	accaattgct	gtaggagaat	ctgactttga	aaattttaac	acggaagact	3660
ttagtagtga	atcggatctg	gaagaaagca	aagagaaact	gaatgaaagc	agtagctcat	3720
cagaaggtag	cactgtggac	atcggcgcac	ctgtagaaga	acagcccgtg	gtggaacctg	3780
aagaaactct	tgaaccagaa	gcttggtttca	ctgaaggctg	tgtacaaaga	ttcaagtgtt	3840
gtcaaataca	tgtggaagaa	ggcagaggaa	aacaatggtg	gaacctgaga	aggacgtgtt	3900
tccgaatagt	tgaacataac	tggtttgaga	ccttcattgt	tttcatgatt	ctccttagta	3960
gtggtgctct	ggcattttgaa	gatatatata	ttgatcagcg	aaagacgatt	aagacgatgt	4020
tggaaatagc	tgacaagggt	ttcacttaca	ttttcattct	ggaaatgctt	ctaaaatggg	4080
tggcatatgg	ctatcaaaca	tatttcacca	atgcctggtg	ttggctggac	ttcttaattg	4140
ttgatgtttc	attggtcagt	ttaacagcaa	atgccttggg	ttactcagaa	cttgagacca	4200
tcaaatactct	caggacacta	agagctctga	gacctctaag	agccttatct	cgatttgaag	4260
ggatgagggt	ggttgtgaat	gcccttttag	gagcaattcc	atccatcatg	aatgtgcttc	4320
tggtttgtct	tatattctgg	ctaattttca	gcatcatggg	cgtaaatttg	tttgctggca	4380
aattctacca	ctgtattaac	accacaactg	gtgacagggt	tgacatcgaa	gacgtgaata	4440
atcatactga	ttgcctaaaa	ctaatagaaa	gaaatgagac	tgctcgatgg	aaaaatgtga	4500
aagtaaactt	tgataatgta	ggatttgggt	atctctcttt	gcttcaagtt	gccacattca	4560
aaggatggat	ggatataatg	tatgcagcag	ttgattccag	aaatgtggaa	ctccagccta	4620
agtatgaaaa	aagtctgtac	atgtatcttt	actttgttat	tttcatcatc	tttgggtcct	4680
tcttcacctt	gaacctgttt	attggtgtca	tcatagataa	tttcaaccag	cagaaaaaga	4740
agtttggagg	tcaagacatc	tttatgacag	aagaacagaa	gaaatactat	aatgcaatga	4800
aaaaattagg	atcgaaaaaa	ccgcaaaaagc	ctatacctcg	accaggaaac	aaatttcaag	4860
gaatggtctt	tgacttcgta	accagacaag	tttttgacat	aagcatcatg	attctcatct	4920
gtcttaacat	ggtcacaatg	atggtggaaa	cagatgacca	gagtgaatat	gtgactacca	4980
ttttgtcacg	catcaatctg	gtgttcattg	tgctatttac	tggagagtgt	gtactgaaac	5040
tcattctctc	acgccattat	tattttacca	ttggatggaa	tatttttgat	tttgtggttg	5100
tcattctctc	cattgtaggt	atgtttcttg	ccgagctgat	agaaaagtat	ttcgtgtccc	5160
ctaccctgtt	ccgagtgatc	cgtcttgcta	ggattggccg	aatcctacgt	ctgatcaaag	5220
gagcaaaggg	gatccgcacg	ctgctctttg	ctttgatgat	gtcccttcct	gcgttgttta	5280
acatcggcct	cctactcttc	ctagtcatgt	tcattctacgc	catctttggg	atgtccaact	5340
ttgcctatgt	taagagggaa	gttgggatcg	atgacatggt	caactttgag	acctttggca	5400
acagcatgat	ctgcctattc	caaattacaa	cctctgctgg	ctgggatgga	ttgctagcac	5460
ccattctcaa	cagtaagcca	cccgactgtg	accctaataa	agttaaccct	ggaagctcag	5520
ttaagggaga	ctgtgggaac	ccatctgttg	gaattttctt	ttttgtcagt	tacatcatca	5580
tatccttcct	ggttgtggtg	aacatgtaca	tgcggtcat	cctggagAAC	ttcagtgttg	5640
ctactgaaga	aagtgcagag	cctctgagtg	aggatgactt	tgagatgttc	tatgaggttt	5700
gggagaagtt	tgatcccgat	gcaactcagt	tcattggaatt	tgaaaaatta	tctcagtttg	5760
cagctgcgct	tgaaccgcct	ctcaatctgc	cacaaccaaa	caaactccag	ctcattgcca	5820
tggatttgcc	catggtgagt	ggtgaccgga	tccactgtct	tgatatctta	tttgctttta	5880
caaagcgggt	tctaggagag	agtggagaga	tggatgctct	acgaatacag	atggaagagc	5940
gattcatggc	ttccaatcct	tccaagggtct	cctatcagcc	aatcactact	actttaaaac	6000
gaaaacaaga	ggaagtatct	gctgtcatta	ttcagcgtgc	ttacagacgc	caccttttaa	6060
agcgaactgt	aaaacaagct	tcctttacgt	acaataaaaa	caaaatcaaa	ggtggggcta	6120
atcttcttat	aaaagaagac	atgataattg	acagaataaa	tgaaaactct	attacagaaa	6180
aaactgatct	gaccatgtcc	actgcagctt	gtccaccttc	ctatgaccgg	gtgacaaagc	6240
caattgtgga	aaaacatgag	caagaaggca	aagatgaaaa	agccaaaggg	aaataaatga	6300
aaataaataa	aaataattgg	gtgacaaatt	gtttacagcc	tgtgaagggtg	atgtattttt	6360
atcaacagga	ctccttttagg	aggtcaatgc	caaactgact	gtttttacac	aaatctcctt	6420
aaggtcagtg	cctacaataa	gacagtgacc	ccttgctcagc	aaactgtgac	tctgtgtaaa	6480
ggggagatga	ccttgacagg	aggttactgt	tctcactacc	agctgacact	gctgaagata	6540
agatgcacaa	tggctagtca	gactgtaggg	accagtttca	aggggtgcaa	acctgtgatt	6600
ttgggggttg	ttaacatgaa	acacttttagt	gtagtaattg	tatccactgt	ttgcatttca	6660
actgccacat	ttgtcacatt	tttatggaa	ctgttagtgg	attcatcttt	ttgttaatcc	6720
atgtgtttat	tatatgtgac	tattttttgta	aacgaagtgt	ctgttgagaa	ataggctaag	6780
gacctctata	acaggtatgc	cacctggggg	gtatggcaac	cacatggccc	tcccagctac	6840
acaaagtcgt	ggtttgcatg	agggcatgct	gcacttagag	atcatgcatg	agaaaaagtc	6900
acaagaaaaa	caaattctta	aattttacca	tattttctggg	aggggttaatt	gggtgataag	6960

tggaggtgct	ttgttgatct	tgttttgcca	aatccagccc	ctagaccaag	tagattat	7020
gtgggtaggc	cagtaaatct	tagcaggtgc	aaacttcatt	caaagtgttg	gagtcataaa	7080
tgttatgttt	ctttttgttg	tattaaaaaa	aaaacctgaa	tagtgaatat	tgccccctcac	7140
cctccaccgc	cagaagactg	aattgaccaa	aattactctt	tataaatttc	tgctttttcc	7200
tgcactttgt	ttagccatct	ttgggctctc	agcaagggtg	acactgtata	tgttaatgaa	7260
atgctattta	ttatgtaa	agtcatttta	ccctgtggtg	cacgtttgag	caaacaaata	7320
atgacctaa	cacagtattt	attgcatcaa	atatgtacca	caagaaatgt	agagtgcagg	7380
ctttacacag	gtaataaa	gtattctgta	ccatttatag	atagtttgga	tgctatcaat	7440
gcatgtttat	attaccatgc	tgctgtatct	ggtttctctc	actgctcaga	atctcattta	7500
tgagaaacca	tatgtcagtg	gtaaagtcaa	ggaaattggt	caacagatct	catttattta	7560
agtcattaag	caatagtttg	cagcacttta	acagcttttt	ggttattttt	acattttaag	7620
tggataacat	atggtatata	gccagactgt	acagacatgt	ttaaaaaac	acactgctta	7680
acctattaaa	tatgtgttta	gaattttata	agcaaata	aatactgtaa	aaagtcactt	7740
tattttat	ttcagcatta	tgtacataaa	tatgaagagg	aaattatctt	cagggtgata	7800
tcacaatcac	ttttcttact	ttctgtccat	agtacttttt	catgaaagaa	atttgctaaa	7860
taagacatga	aaacaagact	gggtagttgt	agatttctgc	tttttaaatt	acatttgcta	7920
attttagatt	atttcacaat	tttaaggagc	aaaatagggt	cacgattcat	atccaaatta	7980
tgctttgcaa	ttggaaaagg	gtttaaaatt	ttatttatat	ttctggtagt	acctgtacta	8040
actgaattga	aggtagtgct	tatgttattt	ttgttctttt	tttctgactt	cggtttatgt	8100
tttcatttct	ttggagtaat	gctgctctag	attgttctaa	atagaatgtg	ggcttcataa	8160
tttttttttc	cacaaaaaca	gagtagtcaa	cttatatagt	caattacatc	aggacatttt	8220
gtgtttctta	cagaagcaaa	ccataggctc	ctcttttcct	taaaactact	tagataaact	8280
gtattcgtga	actgcatgct	ggaaaatgct	actattatgc	taaataatgc	taaccaacat	8340
ttaaaatgtg	caaaactaat	aaagattaca	ttttttat	t		8381

77748-6

-41-

CLAIMS:

1. An isolated nucleic acid molecule encoding a mutant alpha-1 subunit of a mammalian voltage-gated sodium channel, wherein a point mutation has occurred and said mutation disrupts the functioning of an assembled sodium channel so as to produce an epilepsy phenotype, said nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 5.
2. An isolated nucleic acid molecule consisting of the nucleotide sequence set forth in SEQ ID NO: 5.
3. An isolated polypeptide, said polypeptide being a mutant alpha-1 subunit of a mammalian voltage-gated sodium channel, wherein a substitution has occurred and said substitution disrupts the functioning of an assembled sodium channel so as to produce an epilepsy phenotype, said polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 6.
4. An isolated polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 6.
5. An assembled mammalian voltage-gated sodium channel comprising the polypeptide as claimed in claim 3 or 4.
6. A cell transformed with the isolated nucleic acid molecule as claimed in claim 1 or 2.
7. The cell as claimed in claim 6 which is an eukaryotic cell or bacterial cell.
8. A method of preparing the polypeptide as claimed in claim 3 or 4 comprising the steps of:
 - (1) culturing the cell as claimed in claim 6 or 7 under conditions effective for polypeptide production; and

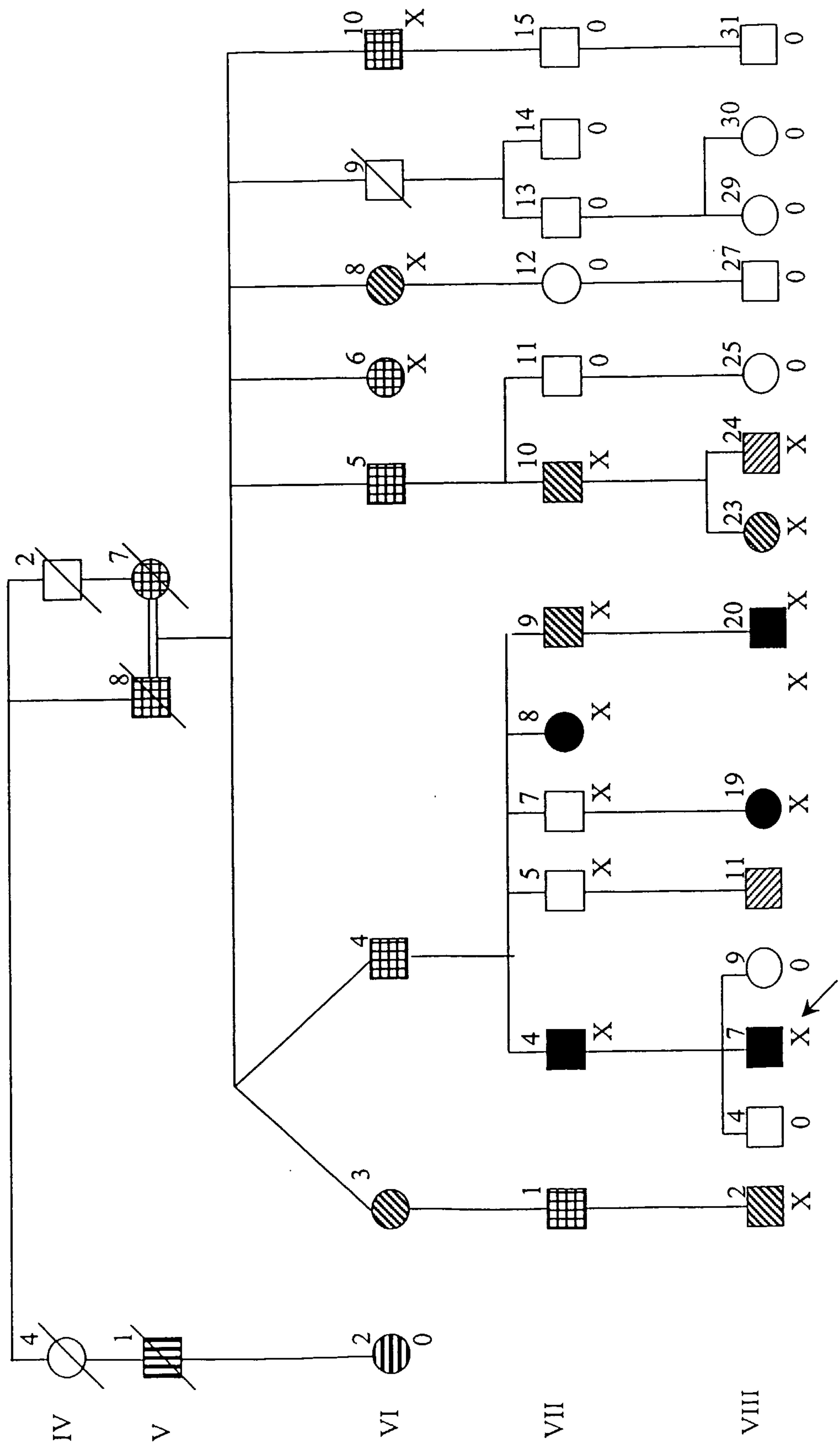
77748-6

-42-

(2) harvesting the polypeptide.

9. An antibody that specifically binds the polypeptide as defined in claim 3 or 4, but not a wild-type mammalian voltage-gated sodium channel.
10. An expression vector comprising the nucleic acid molecule as claimed
5 in claim 1 or 2.
11. Use of the nucleic acid molecule as claimed in claim 1 or 2 in the diagnosis of generalised epilepsy with febrile seizures plus.
12. Use of the polypeptide as defined in claim 3 or 4 in the diagnosis of generalised epilepsy with febrile seizures plus.
- 10 13. Use of the antibody as claimed in claim 9 in the diagnosis of generalised epilepsy with febrile seizures plus.
14. The isolated nucleic acid molecule as claimed in claim 1 or 2 for use in the diagnosis of generalised epilepsy with febrile seizures plus.
15. The isolated polypeptide as claimed in claim 3 or 4 for use in the
15 diagnosis of generalised epilepsy with febrile seizures plus.
16. The antibody as claimed in claim 9 for use in the diagnosis of generalised epilepsy with febrile seizures plus.
17. The antibody as claimed in claim 9 or 16 which is a polyclonal antibody.
18. A monoclonal antibody that specifically binds the polypeptide as defined
20 in claim 4, but not a wild-type mammalian voltage-gated sodium channel.

Figure 1A



2/5

Figure 1B

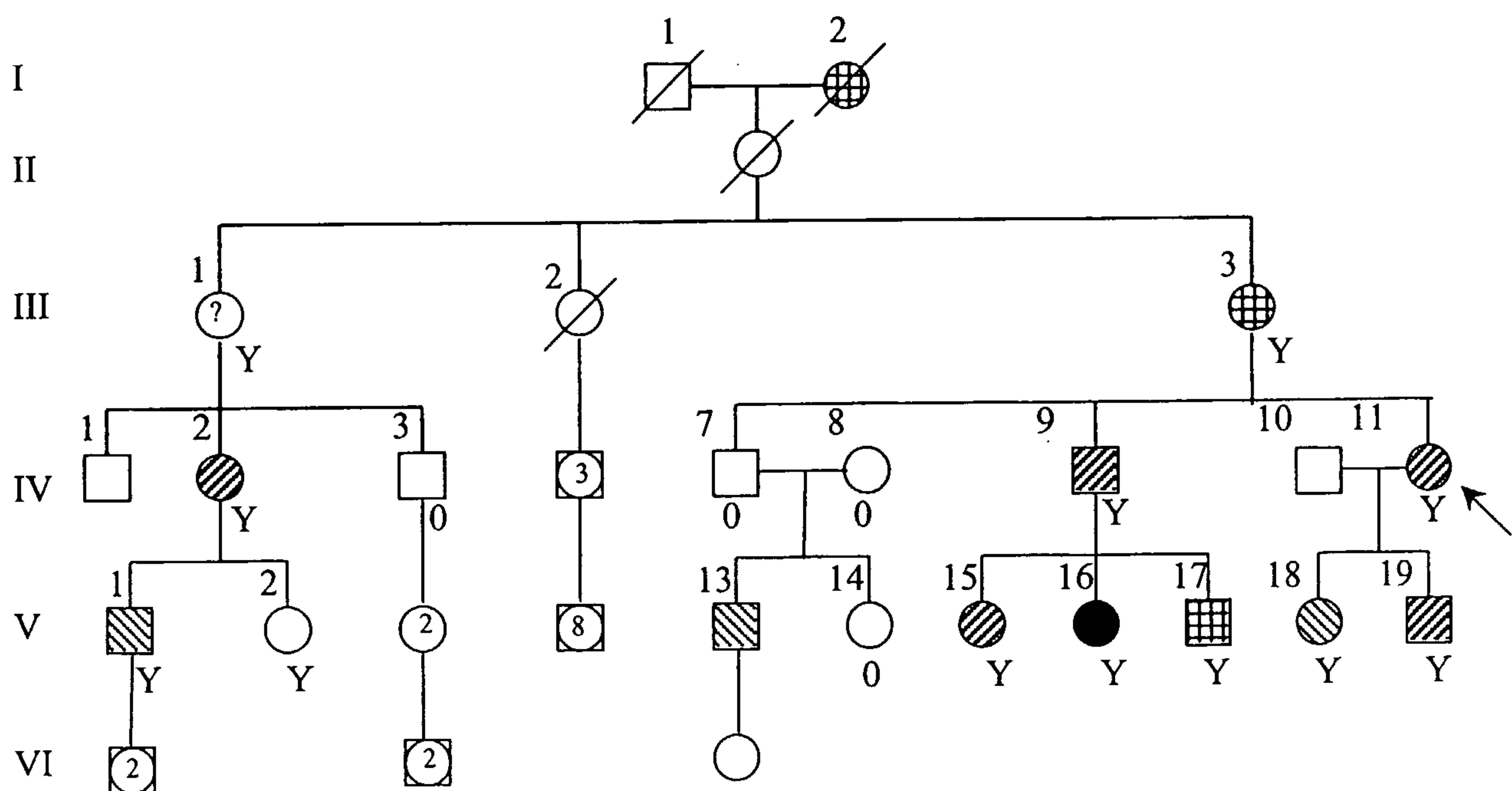
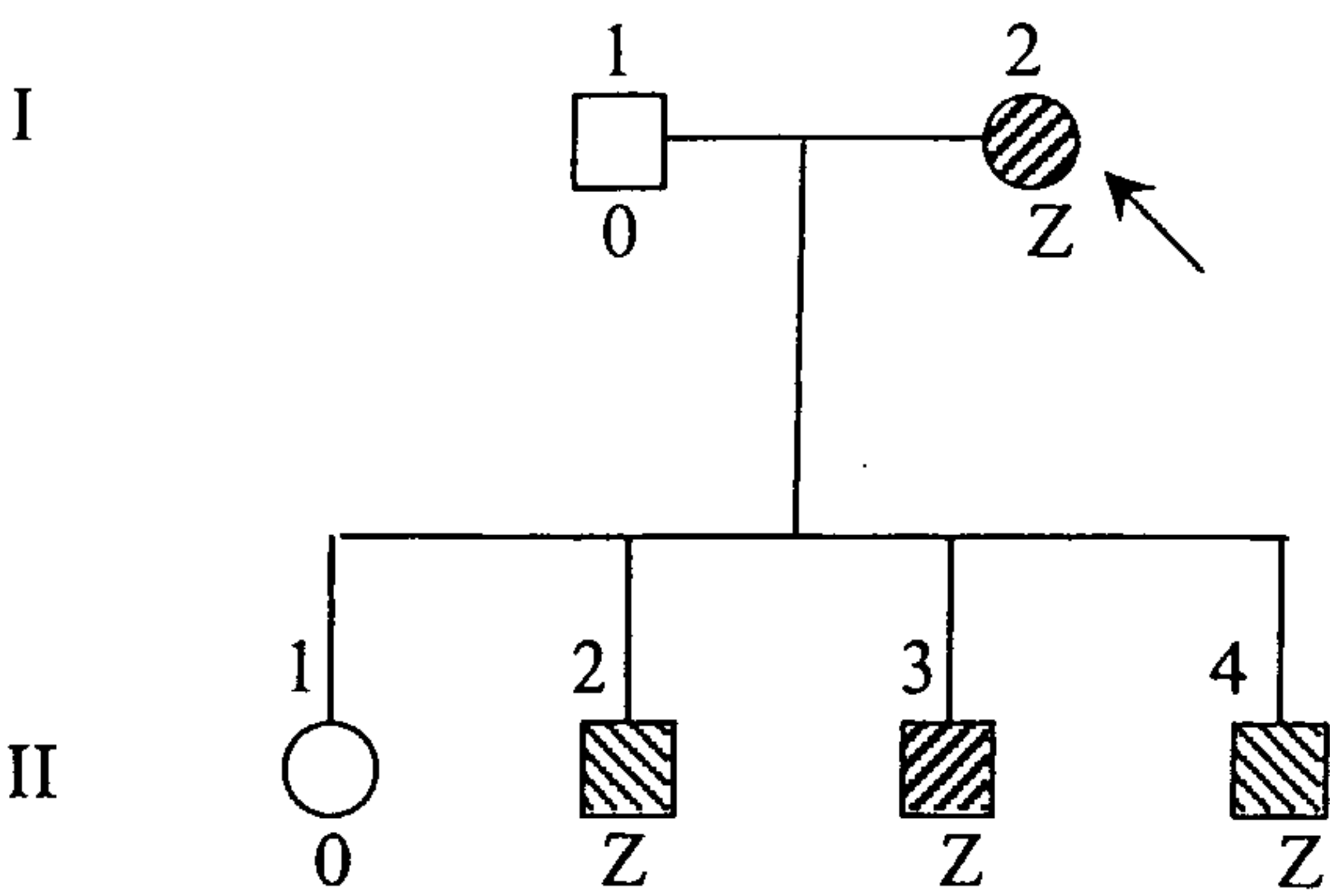
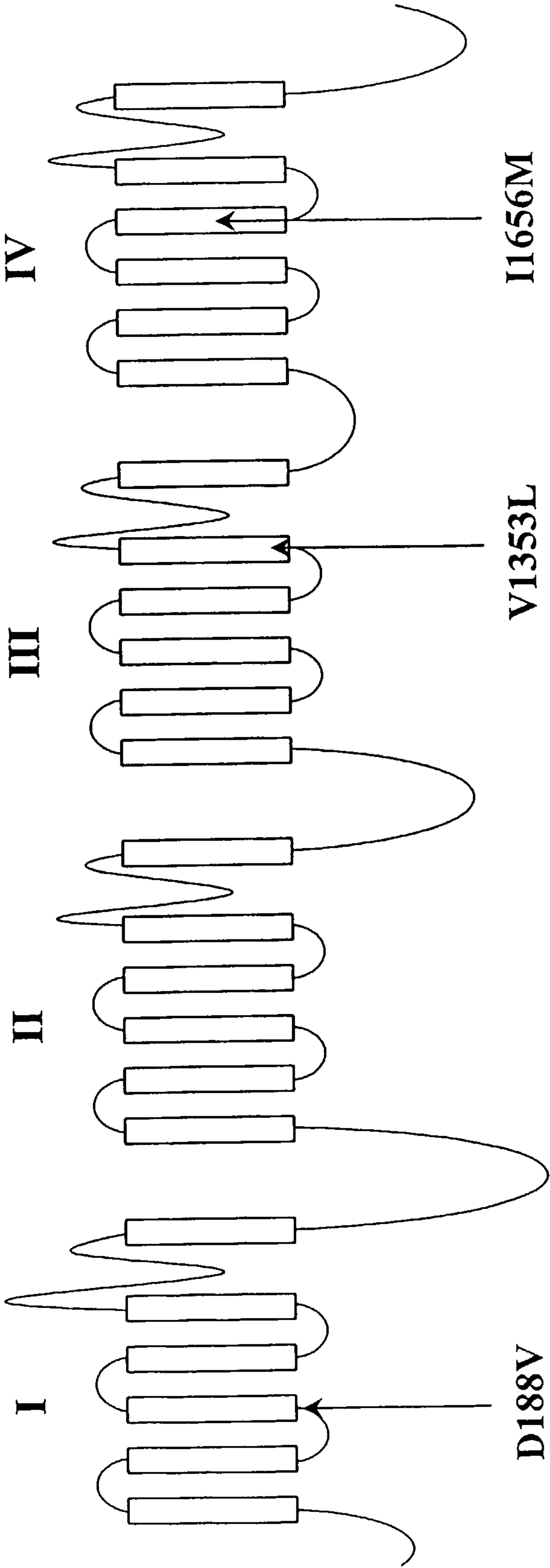


Figure 1C



	febrile seizures (FS)	X	D188V
	febrile seizures plus (FS+)	Y	V1353L
	FS+, extended phenotype	Z	I1656M
	Unclassified	0	no mutation
	Partial epilepsy		
	Juvenile myoclonic epilepsy		

Figure 2



5/5

Figure 3

i) D188V

	F	T	F	L	R	D	P	W	N	W	L
SCN1A	-	-	-	-	-	-	-	-	-	-	-
RAT SCN1A	-	-	-	-	-	-	-	-	-	-	-
SCN2A	-	-	-	-	-	-	-	-	-	-	-
SCN3A	-	-	-	-	-	-	-	-	-	-	-
SCN4A	-	-	-	-	-	-	-	-	-	-	-
SCN5A	-	-	-	-	-	-	-	-	-	-	-
SCN6A	-	S	-	-	G	-	-	-	-	-	-
SCN8A	-	-	-	-	-	-	-	-	-	-	-
SCN9A	-	-	-	-	-	-	-	-	-	-	-
SCN10A	-	-	Y	-	-	-	-	-	-	-	-
SCN11A	-	S	-	-	-	-	-	-	-	-	-
SCN12A	-	S	-	-	-	-	-	-	-	-	-
EL. EEL	-	-	-	-	-	-	-	-	-	-	-
DROS	-	-	Y	-	-	-	A	-	-	-	-
SQUID	-	-	Y	-	-	-	A	-	-	-	-
FLATWORM	-	-	Y	-	-	S	I	-	-	-	-
JELLYFISH	Y	S	Y	-	-	N	S	-	-	-	-

ii) V1353L

	M	N	V	L	L	V	C	L	I	F	W
SCN1A	-	-	-	-	-	-	-	-	-	-	-
RAT SCN1A	-	-	-	-	-	-	-	-	-	-	-
SCN2A	-	-	-	-	-	-	-	-	-	-	-
SCN3A	-	-	-	-	-	-	-	-	-	-	-
SCN4A	-	-	-	-	-	-	-	-	-	-	-
SCN5A	-	-	-	-	-	-	-	-	-	-	-
SCN6A	L	-	-	F	-	-	-	-	M	I	-
SCN8A	-	-	-	-	-	-	-	-	-	-	-
SCN9A	-	-	-	-	-	-	-	-	-	-	-
SCN10A	-	-	-	-	-	-	-	-	-	-	-
SCN11A	L	-	-	-	-	-	-	-	-	-	-
SCN12A	L	-	-	-	-	-	-	-	-	-	-
EL. EEL	-	-	-	-	-	-	-	-	-	-	-
DROS	F	-	-	-	-	-	-	-	-	-	-
SQUID	F	-	-	-	-	-	-	-	V	-	-
FLATWORM	F	-	-	M	V	-	-	-	V	-	-
JELLYFISH	A	-	-	-	-	-	-	G	V	-	-

iii) I1656M

	K	G	A	K	G	I	R	T	L	L	F
SCN1A	-	-	-	-	-	-	-	-	-	-	-
RAT SCN1A	-	-	-	-	-	-	-	-	-	-	-
SCN2A	-	-	-	-	-	-	-	-	-	-	-
SCN3A	-	-	-	-	-	-	-	-	-	-	-
SCN4A	R	-	-	-	-	-	-	-	-	-	-
SCN5A	R	-	-	-	-	-	-	-	-	-	-
SCN6A	-	-	P	-	V	F	H	N	-	M	L
SCN8A	-	-	-	-	-	-	-	-	-	-	-
SCN9A	-	-	-	-	-	-	-	-	-	-	-
SCN10A	R	A	-	-	-	-	-	-	-	-	-
SCN11A	R	A	-	-	-	-	-	-	-	-	-
SCN12A	R	A	-	-	-	-	-	-	-	-	-
EL. EEL	-	-	-	-	-	-	-	-	-	-	-
DROS	-	-	-	-	-	-	-	-	-	-	-
SQUID	-	S	-	-	-	-	-	-	-	-	-
FLATWORM	-	S	-	R	-	-	-	-	-	-	-
JELLYFISH	D	-	-	-	-	-	-	Q	-	-	-

