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(54) Title: ISOLATED LAMININ 10

(57) Abstract: The present invention provides isolated laminin 10, methods for making recombinant laminin 10, host cells that express recombinant laminin 10, and methods for using the recombinant laminin 10 to accelerate the healing of injuries to vascular tissue, and to promote cell attachment and migration. The present invention also provides nucleic acid sequences encoding full length human laminin $\alpha 5$ chain, expression vectors and host cells thereof, and isolated full length human laminin $\alpha 5$ polypeptide chain.



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ISOLATED LAMININ 10

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10 Field of the Invention

This application relates to cell biology, molecular biology, proteins, nucleic acids, and laminins.

Background of the Invention

15 Basal laminae (basement membranes) are sheet-like, cell-associated extracellular matrices that play a central role in cell growth, tissue development, and tissue maintenance. They are present in virtually all tissues, and appear in the earliest stages of embryonic development.

Basal laminae are central to a variety of architectural and cell-interactive
20 functions (See for example, Malinda and Kleinman, *Int. J. Biochem. Cell Biol.* 28:957-959 (1996); Aumailley and Krieg, *J. Invest. Dermatology* 106:209-214 (1996)). For example:

1. They serve as architectural supports for tissues, providing adhesive substrata
25 for cells.
2. They create perm-selective barriers between tissue compartments that impede the migration of cells and passively regulate the exchange of macromolecules. These properties are illustrated by the kidney glomerular basement membrane, which functions as an important filtration structure, creating an effective
30 blood-tissue barrier that is not permeable to most proteins and cells.
3. Basal laminae create highly interactive surfaces that can promote cell migration and cell elongation during embryogenesis and wound repair.

Following an injury, they provide a surface upon which cells regenerate to restore normal tissue function.

4. Basal laminae present information encoded in their structure to contacting cells that is important for differentiation and tissue maintenance. This information is communicated to the cells through various receptors that include the integrins, dystroglycan, and cell surface proteoglycans. Signaling is dependent not only on the presence of matrix ligands and corresponding receptors that interact with sufficient affinities, but also on such topographical factors as ligand density in a three-dimensional matrix "landscape", and on the ability of basal lamina components to cluster receptors. Because these matrix proteins can be long-lived, basal laminae create a "surface memory" in the basal lamina for resident and transient cells.

The basal lamina is largely composed of laminin and type IV collagen heterotrimers that in turn become organized into complex polymeric structures. To date, six type IV collagen chains and at least twelve laminin subunits have been identified. These chains possess shared and unique functions and are expressed with specific temporal (developmental) and spatial (tissue-site specific) patterns.

Laminins are a family of heterotrimeric glycoproteins that reside primarily in the basal lamina. They function via binding interactions with neighboring cell receptors, and by forming laminin networks, and they are important signaling molecules that can strongly influence cellular function. Laminins are important in both maintaining cell/tissue phenotype as well as promoting cell growth and differentiation in tissue repair and development.

Laminins are large, multi-domain proteins, with a common structural organization. The laminin molecule integrates various matrix and cell interactive functions into one molecule.

A laminin molecule is comprised of an α -, β -, and γ -chain subunit joined together through a coiled-coil domain. Within this structure are identifiable domains that possess binding activity towards other laminin and basal lamina molecules, and membrane-bound receptors. Domains VI, IVb, and IVa form globular structures, and domains V, IIIb, and IIIa (which contain cysteine-rich EGF-like elements) form rod-like structures (Kamiguchi et al., Ann. Rev. Neurosci.

21:97-125 (1998)). Domains I and II of the three chains participate in the formation of a triple-stranded coiled-coil structure (the long arm).

Table 1 shows the individual chains that each laminin type is composed of:

5 **TABLE 1.** Known laminin family members

<i>Protein</i>	<i>Chains</i>
Laminin-1	$\alpha 1\beta 1\gamma 1$
Laminin-2	$\alpha 2\beta 1\gamma 1$
Laminin 3	$\alpha 1\beta 2\gamma 1$
Laminin-4	$\alpha 2\beta 2\gamma 1$
Laminin-5	$\alpha 3\beta 3\gamma 2$
Laminin-6	$\alpha 3\beta 1\gamma 1$
Laminin-7	$\alpha 3\beta 2\gamma 1$
Laminin-8	$\alpha 4\beta 1\gamma 1$
Laminin-9	$\alpha 4\beta 2\gamma 1$
Laminin-10	$\alpha 5\beta 1\gamma 1$
Laminin-11	$\alpha 5\beta 2\gamma 1$
Laminin-12	$\alpha 2\beta 1\gamma 3$

Four structurally-defined family groups of laminins have been identified. The first group of five identified laminin molecules, including laminin 10 all share the $\beta 1$ and $\gamma 1$ chains, and vary by their α -chain composition ($\alpha 1$ to $\alpha 5$ chain). The second group of five identified laminin molecules all share the $\beta 2$ and $\gamma 1$ chain, and again vary by their α -chain composition. The third group of identified laminin molecules has one identified member, laminin 5, with a chain composition of $\alpha 3\beta 3\gamma 2$. The fourth group of identified laminin molecules has one identified member, laminin 12, with the newly identified $\gamma 3$ chain ($\alpha 2\beta 1\gamma 3$).

15 Some progress has been made in elucidating the relationship between domain structure and function (See, for example, Wewer and Engvall, *Neuromusc. Disord.* 6:409-418 (1996)). The overall sequence similarity among the homologous domains in different chains varies, but it is highest in domain VI (thought to play a key role in laminin polymerization), followed by domains V (possibly involved in protein-protein interactions) and III (entactin/nidogen binding; possible cell adhesion sites), and is lowest in domains I, II (both thought to be involved in intermolecular assembly, and containing possible cell adhesion sites), and G. Not all domains are present in all 3 types of chains. The globular G domain (thought to be involved in cell receptor binding) is present only in the α chains. Other domains may not be present in all chains within a certain chain type. For example, domain VI is absent from $\alpha 3$, $\alpha 4$, and $\gamma 2$ chains (Wewer and Engvall, 1996).

As a result of their large size (>600 kD) and unique structure, the laminin molecules can be resolved in the electron microscope (Wewer and Engvall, 1996). Typically, laminins appear as cross-shaped molecules in an EM. The three short arms of the cross represent the amino terminal portions of each of the three separate laminin chains (one short arm per chain). The long arm of the cross is composed of
5 laminin chains (one short arm per chain). The long arm of the cross is composed of the C-terminal parts of the three chains, which together form a coiled coil structure (Wewer and Engvall, 1996). The long arm ends with the globular G domain.

The coiled-coil domain of the long arm is crucial for assembly of the three chains of laminin (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-10194 (1997)).
10 Disulfide bonds bridge and stabilize all three chains in the most proximal region of the long arm and join the β and γ chains in the most distal region of the long arm.

A model of laminin receptor-facilitated self-assembly, based on studies conducted with cultured skeletal myotubes and Schwann cells, predicts that laminins bind to their receptors, which freely diffuse in a fluidic membrane, when ligand-free.
15 Receptor engagement forces the laminins into a high local two-dimensional concentration, facilitating their mass-action driven assembly into ordered surface polymers. In this process, the engaged receptors are also reorganized, accompanied by cytoskeletal rearrangements (Colognato, J. Cell Biol. 145:619-631 (1999)). This reorganization activates the receptors, causing signal transduction with the alteration
20 of cell expression, shape and/or behavior. The evidence is that laminins must possess both cell-interacting and architecture-forming sites, which are located in different protein domains and on different subunits.

One class of laminin receptors are the integrins, which are cell surface receptors that mediate many cell-matrix and cell-cell interactions. Integrins are
25 heterodimers, consisting of an α and a β subunit. 16 α - and 8 β -subunits are known, and at least 22 combinations of α and β subunits have been identified to date. Some integrins have only one or a few known ligands, whereas others appear to be very promiscuous. Binding to integrins is generally of low affinity, and is dependent on divalent cations. Integrins, activated through binding to their ligands, transduce
30 signals via kinase activation cascades, such as focal adhesion and mitogen-activated kinases. Several different integrins bind different laminin isoforms more or less specifically (Aumailley et al., In The Laminins, Timpl and Ekblom, eds., Harwood Academic Publishers, Amsterdam. pp. 127-158 (1996)).

Laminin isoforms are expressed in tissue-specific and developmentally regulated patterns and they play significant roles in adhesion, migration, proliferation and differentiation of many cell types (Timpl, R., and Brown, J.C. (1994) *Matrix Biol.* 14(4), 275-81.; Ekblom, P., Timpl, R. (ed) (1996) *The laminins* Vol. 2. Cell Adhesion & Communication. Edited by Goridis, C., Harwood Academic Publishers GmbH, Amsterdam; Sorokin, L. M., et al. (1997) *Dev. Biol.* 189(2), 285-300.; Aumailley, M., and Smyth, N. (1998) *J. Anat.* 193(Pt 1), 1-21).

The laminin $\alpha 5$ chain, a component of laminin-10 ($\alpha 5\beta 1\gamma 1$) and laminin-11 ($\alpha 5\beta 2\gamma 1$), is expressed widely in adult tissues including placenta, heart, lung, skeletal muscle, kidney, and pancreas (Sorokin, L. M., et al. (1997) *Dev. Biol.* 189(2), 285-300; Patton, B. L., et al. (1997) *J. Cell Biol.* 139(6), 1507-21; Miner, J. H., et al. (1997) *J. Cell Biol.* 137(3), 685-701; Miner, J. H., et al. (1995) *J. Biol. Chem.* 270(48), 28523-6; Sorokin, L. M., et al. (1997) *Dev. Dyn.* 210(4), 446-62). Embryos lacking laminin $\alpha 5$ exhibit several developmental abnormalities, such as exencephaly and syndactyly, as well as dysmorphogenesis of the placental labyrinth and die late in embryogenesis (Miner, J. H., et al. (2000) *Dev. Biol.* 217(2), 278-89; Miner, J. H., et al. (1998) *J. Cell Biol.* 143(6), 1713-23). Laminin $\alpha 5$ chain-containing isoforms may therefore be important in placental endothelial cell migration and blood vessel branching, and in formation of proper basal laminae.

Integrin-mediated recognition of ECM molecules results in intracellular signaling that affects a range of cell behaviors (Clark, E. A. et al., *Science* 268(5208), 233-9 (1995)). In endothelial cells, these signals affect focal adhesions and cytoskeletal organization. Therefore, integrin-mediated endothelial cell recognition of laminin and other BM molecules may determine cell-to-matrix adhesiveness and mediate signals that are essential for the maintenance and normal functioning of blood vessels (Davis, G. E. et al., *Exp. Cell Res.* 216(1), 113-23 (1995); Dejana, E. et al., *Kidney Int.* 43(1), 61-5 (1993); and Shattil, S.J. et al., *J. Clin. Invest.* 100(11 Suppl), S91-5 (1997)). Laminin-8 and laminin-10 are secreted by endothelial cells, and are major components of the subendothelial basement membrane (Sorokin, L.M. et al., *Dev. Biol.* 189(2), 285-300 (1997); Iivanainen, A. et al., *J. Biol. Chem.* 272(44), 27862-8 (1997); Patton, B. L. et al., *J. Cell Biol.* 139(6), 1507-21 (1997), Miner, J.H. et al., *J. Cell Biol.* 137(3), 685-701 (1997); Sorokin, L. et al., *Eur. J. Biochem.* 223(2), 603-10 (1994); and Tokida, Y. et al., *J. Biol. Chem.* 265(30), 18123-9 (1990)).

There have been no reports of isolated laminin 10 that is free of other laminin chains. Studies on the function of laminin-10 have frequently used commercial preparations, which are normally prepared using proteolytic digestion and subsequent immunoaffinity chromatography resulting in a truncated mixture of $\alpha 5$ -chain containing laminin isoforms (Sixt, M. et al., J. Biol. Chem. 276(22), 18878-87 (2001)). Attempts to purify laminin 10 from cell sources by affinity chromatography using laminin chain antibodies have been unsuccessful in eliminating, for example, laminin $\beta 2$ chain, which is a component of laminin 11. (See, for example, Sixt, M. et al., J. Biol. Chem. 276(22), 18878-87 (2001)) Thus, such preparations represent a mixture of laminin 10 and laminin 11.

Despite the broad tissue distribution of the laminin $\alpha 5$ chain and laminin 10, the full length human laminin $\alpha 5$ chain sequence is not known, nor is there a means to isolate laminin 10 away from other laminins, nor has a means for recombinant expression of laminin 10 previously been developed. Isolated laminin 10 would have numerous research and therapeutic purposes including, but are not limited to, treating injuries to vascular tissue, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, and preparing improved cell culture devices and media.

Thus, there is a need in the art for isolated laminin-10 for research and therapeutic purposes, and methods for making isolated laminin 10.

Summary of the Invention

In one aspect, the present invention provides an isolated nucleic acid encoding a full-length human laminin $\alpha 5$ chain consisting of the nucleic acid sequence of SEQ ID NO:1, or the complement thereof, as well as vectors comprising the sequence, and host cells transfected with such vectors. In another aspect, the present invention provides isolated laminin $\alpha 5$ chain protein consisting of the amino acid sequence of SEQ ID NO:2.

In another aspect, the present invention provides isolated laminin 10, and methods for producing isolated laminin 10. In a further aspect, the present invention provides recombinant host cells that express laminin 10 chains and secrete recombinant laminin 10.

In a further aspect, the present invention provides pharmaceutical compositions, comprising isolated laminin 10 together with a pharmaceutically acceptable carrier. Such pharmaceutical compositions can optionally be provided with other extracellular matrix components.

5 In another aspect, the present invention provides methods and kits for accelerating the healing of injuries to vascular tissue, and for improving the biocompatibility of grafts used for treating such injuries. In specific examples, laminin 10 or pharmaceutical compositions thereof are used to:

- 10 a. promote re-endothelialization at the site of vascular injuries;
- b. improve the “take” of grafts;
- c. improve the biocompatibility of medical devices; and/or
- d. promote cell attachment and subsequent cell stasis, proliferation, differentiation, and/or migration.

by providing an amount effective of isolated laminin 10 for the various
15 methods. In preferred embodiments of all of these methods, recombinant laminin 10 is used. The kits comprise an amount of isolated laminin 10, or pharmaceutical compositions thereof, effective for the desired effect, and instructions for the use thereof.

In a further aspect, the present invention provides improved medical devices
20 and grafts, wherein the improvement comprises providing medical devices and grafts with an amount effective of isolated laminin 10, or a pharmaceutical composition of the invention.

In a further aspect, the invention provides improved cell culture devices, and
25 methods for preparing improved cell culture devices, for the growth and maintenance of cells in culture, by providing an amount effective to a cell culture device of isolated laminin 10 for cell attachment and subsequent cell stasis, proliferation, differentiation, and/or migration.

30 **Brief Description of the Figures**

Figure 1. cDNA-derived amino acid sequence of the human laminin 5 chain and alignment with the mouse chain. Upper sequence, human $\alpha 5$ chain; Lower sequence, mouse sequence. Domain boundaries are depicted, and adhesive tripeptide

sequences RGD and LRE are boxed. The potential cleavage site of the signal peptide is indicated by a solid triangle (Predicted by PSORT II). The five possible polymorphisms are shown as bold italic characters above the human sequence. The sequence submitted to GenBank by the Human Genome Project (accession
5 NM_005560 (May 30, 2001)) differed from the present sequence at a few sites, indicated above the sequence in the figure. At these sites, the present sequence did not differ from the incomplete genomic sequences reported by Celera.

Figure 2. Characterization of r-laminin-10 using SDS-PAGE. (A) Silver stain:
10 Conditioned medium of triple-transfected HEK293 cells (CM) and recombinant purified laminin-10 (r-laminin-10), were analyzed by SDS-PAGE on 4-15% gradient gels under reducing conditions; (B) Immunoblot of CM and r-laminin-10 under reducing conditions: Separated proteins on 5% gels were transferred onto PVDF membranes followed by staining with mAbs against laminin α 5 (15H5), β 1 (DG10),
15 γ 1 (clone 22) and FLAG-M2.; (C) Silver stain and immunoblot of rLN-10 under non-reducing conditions: Separated proteins on 5% gels were visualized by silver staining or transferred onto PVDF membranes followed by staining with mAbs against laminin α 5 (15H5), β 1 (DG10), γ 1 (2E8). The positions of molecular size markers are shown.

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Figure 3. Cell adhesion activity of recombinant laminin-10 (rLN-10) and other proteins. (A) HT-1080 cell adhesion to rLN-10, recombinant laminin-8 (rLN-8), laminin-1/nidogen complex (LN-1/Nd), and fibronectin (FN) coated at increasing concentrations.; (B) IBE cell adhesion to rLN-10, rLN-8, LN-1/Nd, and FN coated at
25 increasing concentrations.; (C) HSVEC adhesion to rLN-10 and rLN-8 coated at 3 and 10 mg/ml, and LN-1/Nd, commercial laminin-10/11 (LN-10/11), collagen type IV (Col IV) and FN coated at 10 mg/ml. N.T. means not-tested. Bound cells were quantitated spectrophotometrically using adhesion to BSA as blank. Error bars indicate S.D.

30

Figure 4. HT-1080 cell and HSVEC adhesion assays on laminins coated at 10 g/ml. Text under columns indicate the integrin subunit mAbs used or other added

substances. Adhesion shown is relative to control, designated 100. Adhesion to BSA was designated zero. Error bars indicate S.D.

Figure 5. HSVEC migration (endothelialization) on plastic coated with laminin-10 and other proteins. Migration of HSVECs into the cell free area coated with BSA, laminin-1/ nidogen complex (LN-1/Nd), recombinant laminin-8 (rLN-8), recombinant laminin-10 (rLN-10), fibronectin (FN), commercial laminin-10/11 (LN-10/11), gelatin, and collagen type IV (Col IV) was measured. The distance covered by cells from three different donors. N.T. means not-tested.

10

Table 2: Primers used in laminin 5 expression construct preparation.

Upper row, forward primer; Lower row, reverse primer.

plasmid	primer	primer sequence
KBX3	KZK1	5'-gccaccatggcgaagcggctctg-3' (SEQ ID NO.:21)
	Ba3r	5'-aagggcaggatccactgggg-3' (SEQ ID NO.:22)
BBL3	Bam4	5'-ctactgcgaagctggctctt-3' (SEQ ID NO.:23)
	Bcl1r	5'-ccaggtggctctgggtatc-3' (SEQ ID NO.:24)
BNK2'	Bcl2	5'-gcgacaactgcctcctctac-3' (SEQ ID NO.:25)
	Not4r	5'-agtgggttcccaaagaatcc-3' (SEQ ID NO.:26)
BNL12	Bpu1F	5'-cctctgtgacgagctcacg-3' (SEQ ID NO.:27)
	Not4r	5'-agtgggttcccaaagaatcc-3' (SEQ ID NO.:26)
D29D301	D29	5'-gatgtgccctgtcagtgccat-3' (SEQ ID NO.:28)
	D301	5'-tgtcgtgttcagccgcttgaggt-3' (SEQ ID NO.:29)
NSK5	Not3	5'-ctctcagtcctccaacaac-3' (SEQ ID NO.:30)
	Sal4r	5'-ctgactgtcgaagctgatgc-3' (SEQ ID NO.:31)
SFK2	Sal5	5'-ggaggtggtcagcctctaca-3' (SEQ ID NO.:32)
	FLAG1	5'-ttactgtcatcgtcgtccttgtagtcggcggtgggcag-3' (SEQ ID NO.:33)
SFL13	Sal5	5'-ggaggtggtcagcctctaca-3' (SEQ ID NO.:32)
	m19R	5'-aatggtgccagactcagg-3' (SEQ ID NO.:34)

Detailed Description of the Preferred Embodiments

15

All references, patents and patent applications are hereby incorporated by reference in their entirety.

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press),
5 *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutscher, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press,
10 San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

In one aspect, the present invention provides an isolated nucleic acid encoding
15 a full length laminin $\alpha 5$ chain polypeptide consisting of the amino acid sequence of SEQ ID NO:2. In a preferred embodiment, the isolated nucleic acid consists of the sequence of SEQ ID NO:1, the complement thereof, or the RNA expression product thereof.

In an additional aspect, the present invention provides an isolated nucleic acid
20 comprising a nucleic acid sequence encoding the 2,743 N-terminal amino acids (SEQ ID NO:36) of the human laminin $\alpha 5$ chain, which has not previously been reported. In a preferred embodiment, the isolated nucleic acid consists of the sequence of SEQ ID NO:35, the complements thereof, or the RNA expression product thereof.

An used herein, an "isolated nucleic acid sequence" refers to a nucleic acid
25 sequence that is free of gene sequences which naturally flank the nucleic acid in the genomic DNA of the organism from which the nucleic acid is derived (i.e., genetic sequences that are located adjacent to the gene for the isolated nucleic molecule in the genomic DNA of the organism from which the nucleic acid is derived). An "isolated" laminin $\alpha 5$ chain nucleic acid sequence according to the present invention may,
30 however, be linked to other nucleotide sequences that do not normally flank the recited sequence, such as a heterologous promoter sequence, or other vector sequences. It is not necessary for the isolated nucleic acid sequence to be free of other cellular material to be considered "isolated", as a nucleic acid sequence

according to the invention may be part of an expression vector that is used to transfect host cells (see below).

In another aspect, the present invention provides recombinant expression vectors comprising a full length laminin α 5 chain nucleic acid sequence, or a nucleic acid sequence expressing the 2,743 N-terminal amino acids (SEQ ID NO:36) of the human laminin α 5 chain. In one embodiment, the expression vectors comprise a nucleic acid encoding a polypeptide selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:36, operatively linked to a heterologous (i.e.: is not the naturally occurring α 5 laminin chain promoter) promoter. In a preferred embodiment, the isolated nucleic acid consists of a sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:35. A promoter and a laminin α 5 chain nucleic acid sequence are "operatively linked" when the promoter is capable of driving expression of the laminin α 5 chain DNA into RNA.

As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA into which additional DNA segments may be cloned. Another type of vector is a viral vector, wherein additional DNA segments may be cloned into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors), are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" or simply "expression vectors". In the present invention, the expression of the laminin polypeptide sequence is directed by the promoter sequences of the invention, by operatively linking the promoter sequences of the invention to the gene to be expressed. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably, as the plasmid is the most commonly used form of vector. However, the invention is intended to include other forms of expression vectors, such as viral

vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The vector may also contain additional sequences, such as a polylinker for subcloning of additional nucleic acid sequences, or a polyadenylation signal to effect proper polyadenylation of the transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and any such sequence may be employed, including but not limited to the SV40 and bovine growth hormone poly-A sites. Also contemplated as an element of the vector is a termination sequence, which can serve to enhance message levels and to minimize read through from the construct into other sequences. Additionally, expression vectors typically have selectable markers, often in the form of antibiotic resistance genes, that permit selection of cells that carry these vectors.

In a further embodiment, the present invention provides host cells transfected with the laminin $\alpha 5$ chain-expressing recombinant expression vectors disclosed herein. As used herein, the term "host cell" is intended to refer to a cell into which a nucleic acid of the invention, such as a recombinant expression vector of the invention, has been introduced. Such cells may be prokaryotic, which can be used, for example, to rapidly produce a large amount of the expression vectors of the invention, or may be eukaryotic, for functional studies.

The terms "host cell" and "recombinant host cell" are used interchangeably herein. It should be understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The host cells can be transiently or stably transfected with one or more of the expression vectors of the invention. Such transfection of expression vectors into prokaryotic and eukaryotic cells can be accomplished via any technique known in the art, including but not limited to standard bacterial transformations, calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. (See, for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press; *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY).

In another aspect, the present invention provides an isolated full length human laminin $\alpha 5$ chain polypeptide consisting of amino acid sequence of SEQ ID NO:2. In a further embodiment, of this aspect, the invention provides an isolated polypeptide consisting of the 2,743 N-terminal amino acids (SEQ ID NO:36) of the human
5 laminin $\alpha 5$ chain.

As used herein, an "isolated polypeptide" refers to a polypeptide that is substantially free of other proteins, including other laminin chains, and gel agents, such as polyacrylamide and agarose. In a preferred embodiment, the isolated laminin polypeptide is free of detectable contaminating laminin chains. Thus, the protein can
10 either be isolated from natural sources, or recombinant protein can be isolated from the transfected host cells disclosed above.

In a further aspect, the invention provides methods for detecting the presence of the laminin $\alpha 5$ chain in a protein sample, comprising providing a protein sample to be screened, contacting the protein sample to be screened with an antibody against the
15 2,743 N-terminal amino acids (SEQ ID NO:36) of the human laminin $\alpha 5$ chain, or fragments thereof, and detecting the formation of antibody-antigen complexes.

The antibody can be either polyclonal or monoclonal, although monoclonal antibodies are preferred. As used herein, the term "protein sample" refers to any sample that may contain the laminin $\alpha 5$ chain, including but not limited to tissues and
20 portions thereof, tissue sections, intact cells, cell extracts, purified or partially purified protein samples, bodily fluids, nucleic acid expression libraries. Accordingly, this aspect of the present invention is useful for a variety of purposes including, but not limited to, immunolocalization, immunofluorescence analysis, Western blot analysis, ELISAs, and nucleic acid expression library screening. In one embodiment, the
25 techniques may determine only the presence or absence of the human laminin $\alpha 5$ chain. Alternatively, the techniques may be quantitative, and provide information about the relative amount of laminin $\alpha 5$ chain in the sample. For quantitative purposes, ELISAs are preferred.

Detection of immunocomplex formation between the human laminin $\alpha 5$ chain
30 and antibodies or fragments thereof directed against an amino acid sequence of SEQ ID NO:36, or fragments thereof, can be accomplished by standard detection techniques. For example, detection of immunocomplexes can be accomplished by using labeled antibodies or secondary antibodies.

Antibodies can be made by well-known methods, such as described in Harlow and Lane, *Antibodies; A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., (1988). For example, all or a portion of the amino acid sequence of SEQ ID NO:36, together with an appropriate adjuvant, can be injected
5 into an animal in an amount and at intervals sufficient to elicit an immune response. Animals are bled at regular intervals, preferably weekly, to determine antibody titer. Polyclonal antibodies against laminin α 5 chain can then be purified directly by passing serum collected from the animal through a column to which non-antigen-related proteins prepared from the same expression system without laminin α 5 chain
10 bound.

Monoclonal antibodies can be produced by obtaining spleen cells from the animal. (See Kohler and Milstein, *Nature* 256, 495-497 (1975)). In one example, monoclonal antibodies (mAb) of interest are prepared by immunizing inbred mice with peptide fragments of the amino acid sequence of SEQ ID NO:36. The mice are
15 immunized by the IP or SC route in an amount and at intervals sufficient to elicit an immune response. The mice receive an initial immunization on day 0 and are rested for about 3 to about 30 weeks. Immunized mice are given one or more booster immunizations of by the intravenous (IV) route. Lymphocytes, from antibody positive mice are obtained by removing spleens from immunized mice by standard
20 procedures known in the art. Hybridoma cells are produced by mixing the splenic lymphocytes with an appropriate fusion partner under conditions which will allow the formation of stable hybridomas. The antibody producing cells and fusion partner cells are fused in polyethylene glycol at concentrations from about 30% to about 50%. Fused hybridoma cells are selected by growth in hypoxanthine, thymidine and
25 aminopterin supplemented Dulbecco's Modified Eagles Medium (DMEM) by procedures known in the art. Supernatant fluids are collected from growth positive wells and are screened for antibody production by an immunoassay such as solid phase immunoradioassay. Hybridoma cells from antibody positive wells are cloned
30 by a technique such as the soft agar technique of MacPherson, *Soft Agar Techniques*, in *Tissue Culture Methods and Applications*, Kruse and Paterson, Eds., Academic Press, 1973.

In yet another aspect, the invention provides methods for detecting the presence in a sample of nucleic acid sequences encoding the human laminin α 5 chain, comprising

providing a nucleic acid sample to be screened, contacting the sample with a nucleic acid probe consisting of the nucleic acid sequence of SEQ ID NO:35 or fragments thereof, and detecting complex formation.

As used herein, the term "sample" refers to any sample that may contain
5 nucleic acid sequences encoding the human laminin $\alpha 5$ chain, including but not limited to tissues and portions thereof, tissue sections, intact cells, cell extracts, purified or partially purified nucleic acid samples, DNA libraries, and bodily fluids. Accordingly, this aspect of the present invention may be used to test for the presence of laminin $\alpha 5$ chain mRNA or DNA in these various samples by standard techniques
10 including, but not limited to, in situ hybridization, Northern blotting, Southern blotting, DNA library screening, polymerase chain reaction (PCR) or reverse transcription-PCR (RT-PCR). In one embodiment, the techniques may determine only the presence or absence of the nucleic acid of interest. Alternatively, the techniques may be quantitative, and provide information about the relative amount of
15 the nucleic acid of interest in the sample. For quantitative purposes, quantitative PCR and RT-PCR are preferred. Thus, in one example, RNA is isolated from a sample, and contacted with an oligonucleotide derived from the nucleic acid sequence of SEQ ID NO:35, or its complement, together with reverse transcriptase under suitable buffer and temperature conditions to produce cDNAs from the laminin $\alpha 5$ chain RNA. The
20 cDNA is then subjected to PCR using primer pairs derived from the nucleic acid sequence of interest. For detecting laminin $\alpha 5$ chain nucleic acid sequences, standard labeling techniques can be used to label the probe, the nucleic acid of interest, or the complex between the probe and the nucleic acid of interest, including, but not limited to radio-, enzyme-, chemiluminescent-, or avidin or biotin-labeling
25 techniques, all of which are well known in the art. (See, for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego,
30 CA)).

In another aspect, the present invention provides isolated laminin 10. As used herein "laminin 10" encompasses both r-laminin 10 and heterotrimeric laminin

10 from naturally occurring sources. In a preferred embodiment, the laminin 10 comprises recombinant laminin 10 (or "r-laminin 10").

As used herein, the term "r-laminin 10" refers to recombinant heterotrimeric laminin 10, expressed by a host cell that has been transfected with one or more
5 expression vectors comprising at least one nucleic acid sequence encoding a laminin 10 chain selected from the $\alpha 5$, $\beta 1$ and $\gamma 1$ chains, or processed/secreted forms thereof. Such r-laminin 10 can thus comprise $\alpha 5$, $\beta 1$, and $\gamma 1$ sequences from a single organism, or from different organisms. Various laminin 10 chain DNA sequences are known in the art, and the use of each to prepare the r-laminin 10 of the invention
10 is contemplated. (See, for example, Pouliot, N. et al., *Experimental Cell Research* 261(2):360-71, (2000); Kikkawa, Y. et al., *Journal of Cell Science* 113 (Pt 5):869-76, (2000); Church, HJ. et al., *Biochemical Journal* 332 (Pt 2):491-8, (1998); Sorokin, LM. et al., *Developmental Biology* 189(2):285-300, (1997); Miner, JH. et al., *Journal of Biological Chemistry* 270(48):28523-6, (1995); Sorokin, L. et al., *European*
15 *Journal of Biochemistry* 223(2):603-10, (1994); all references incorporated by reference herein in their entirety). In a preferred embodiment, the r-laminin 10 comprises recombinant human $\alpha 5$, $\beta 1$, and $\gamma 1$ polypeptide chains.

As used herein, "isolated" means that the laminin 10 is substantially free of other proteins, including the laminin $\beta 2$ chain polypeptide chain, and gel agents, such
20 as polyacrylamide and agarose. In a preferred embodiment, the isolated laminin 10 is free of detectable laminin $\beta 2$ polypeptide chains.

The invention encompasses those laminin molecules wherein one or two chains that make up the recombinant heterotrimeric laminin 10 are encoded by endogenous laminin 10 chains. In a preferred embodiment, each of the $\alpha 5$, $\beta 1$, and
25 $\gamma 1$ polypeptide chains are expressed recombinantly.

Laminin 10 is a secreted protein, which is capable of being directed to the endoplasmic reticulum (ER), secretory vesicles, and the extracellular space as a result of a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature"
30 protein. Such processing event can be variable, and thus may yield different versions of the final "mature protein". The isolated laminin 10 of the present invention includes heterotrimers comprising both the full length and any such processed laminin 10 polypeptide chains.

As used herein, a laminin 10 polypeptide chain refers to a polypeptide chain according to one or more of the following:

(a) comprises a polypeptide structure selected from the group consisting of:

1. R1-R2-R3
- 5 2. R1-R2-R3(e)
3. R3
4. R3(e)
5. R1-R3
6. R1-R3(e)
- 10 7. R2-R3
8. R2-R3(e)

wherein R1 is an amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another
15 secreted protein, or an artificial sequence; R3 is a secreted laminin chain selected from group consisting of the $\alpha 5$, $\beta 1$, and $\gamma 1$ chains; and R3(e) is a secreted laminin chain selected from the $\alpha 5$, $\beta 1$, and $\gamma 1$ chains that further comprises an epitope tag (such as those described below), which can be placed at any position within the laminin chain amino acid sequence; and/or

20 (b) is encoded by a polynucleotide that hybridizes under high or low stringency conditions to the coding regions, or portions thereof, of one or more of the recombinant laminin 10 chain DNA sequences disclosed herein (SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, and SEQ ID NO:35), or
25 complementary sequences thereof; and/or

(c) has at least 70% identity to one or more of the disclosed laminin 10 polypeptide chain amino acid sequences (SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, and SEQ ID NO:36), preferably at least 80%
30 identity, and most preferably at least about 90% identity.

“Stringency of hybridization” is used herein to refer to conditions under which nucleic acid hybrids are stable. The invention also includes nucleic acids that hybridize under high stringency conditions (as defined herein) to all or a portion of

the coding sequences of the laminin chain polynucleotides disclosed herein, or their complements. The hybridizing portion of the hybridizing nucleic acids is typically at least 50 nucleotides in length. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T_M) of the hybrids. T_M decreases
5 approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein,
10 high stringency refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

15 Also contemplated are laminin 10-encoding nucleic acid sequences that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt
20 conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following
25 stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and
30 commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

As used herein, "percent identity" of two amino acids or of two nucleic acids is determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul (Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12, to determine nucleotide sequences identity to the nucleic acid molecules of the invention. BLAST protein searches are performed with the XBLAST program, score = 50, wordlength = 3, to determine an amino acid sequence identity to a polypeptide of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (Nucleic Acids. Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used. See <http://www.ncbi.nlm.nih.gov>.

Further embodiments of the present invention include polynucleotides encoding laminin 10 chain polypeptides having at least 70% identity, preferably at least 80% identity, and most preferably at least 90% identity to one or more of the polypeptide sequences contained in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, and SEQ ID NO:36 .

As used herein, " α 5 polynucleotide" refers to polynucleotides encoding an laminin α 5 chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) polynucleotides that encode polypeptides which share at least 70% identity, preferably 80% identity, and most preferably at least 90% identity with one or more sequences selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO:4; (b) the α 5 polynucleotides hybridize under low or high stringency conditions to one or more coding sequences selected from the group consisting of SEQ ID NO: 1 or SEQ ID NO:3; complementary sequences thereof; or (c) the α 5 polynucleotides encode a laminin α 5 chain polypeptide with a general structure selected from the group consisting of (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted α 5 chain polypeptides.

As used herein, " β 1 polynucleotides" refers to polynucleotides encoding a β 1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences selected from the group consisting of SEQ ID NO: 5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12; (b) the β 1 polynucleotides hybridize under low or high stringency conditions to one or more coding sequences selected from the group consisting of SEQ ID NO: 5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, or complementary sequences thereof; or (c) the β 1 polynucleotides encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted β 1 chain polypeptides.

As used herein, " γ 1 polynucleotides" refers to polynucleotides encoding a γ 1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences selected from the group consisting of SEQ ID NO: 14, SEQ ID NO:16, SEQ ID NO:18, or SEQ ID NO:20; (b) the γ 1 polynucleotides hybridize under low or high stringency conditions to one or more of the coding sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19 or complementary sequences thereof; or (c) the γ 1 polynucleotides encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted γ 1 chain polypeptides.

As used herein, the term "epitope tag" refers to a polypeptide sequence that is expressed as part of a chimeric protein, where the epitope tag serves as a recognition site for binding of antibodies generated against the epitope tag, or for binding of other molecules that can be used for affinity purification of sequences containing the tag.

In a preferred embodiment, cDNAs encoding the laminin α 5, β 1 and γ 1 chains, or fragments thereof, are subcloned into an expression vector. Alternatively,

laminin $\alpha 5$, $\beta 1$ and/or $\gamma 1$ gene sequences, including one or more introns, can be used for sub-cloning into an expression vector.

In another aspect, the present invention provides laminin 10 expressing-cells that have been transfected with an expression vector containing promoter sequences
5 that are operatively linked to nucleic acid sequences encoding at least one polypeptide sequence comprising a sequence selected from the group consisting of the $\alpha 5$, $\beta 1$ and $\gamma 1$ chains of laminin 10, wherein the transfected cells secrete heterotrimeric laminin 10 containing the recombinant laminin chain. In a preferred embodiment, the cells are systematically transfected with recombinant expression vectors containing
10 promoter sequences that are operatively linked to nucleic acid sequences encoding polypeptide sequences comprising the $\alpha 5$, $\beta 1$ and $\gamma 1$ chains of laminin 10, even more preferably, all human chains. After the multiple transfections, the cells express recombinant laminin 10 chains, which form the heterotrimeric r-laminin 10.

Transfection of the expression vectors into eukaryotic cells can be
15 accomplished via any technique known in the art, including but not limited to calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Transfection of bacterial cells can be done by standard methods.

In a preferred embodiment, the cells are stably transfected. Methods for stable
20 transfection and selection of appropriate transfected cells are known in the art. In another preferred embodiment, a CMV promoter driven expression vector is used in a human kidney embryonic 293 cell line.

Any cell capable of expressing and secreting the r-laminin 10 can be used. Preferably, eukaryotic cells are used, and most preferably mammalian cells are used,
25 including but not limited to kidney and epithelial cell lines. The promoter sequence used to drive expression of the individual chains or r-laminin 10 may be constitutive (driven by any of a variety of promoters, including but not limited to, CMV, SV40, RSV, actin, EF) or inducible (driven by any of a number of inducible promoters including, but not limited to, tetracycline, ecdysone, steroid-responsive).
30 Carbohydrate and disulfide post-translational modifications are believed to be required for laminin 10 protein folding and function. This makes the use of eukaryotic cells preferable for producing functional r-laminin 10, although other systems are useful for obtaining, for example, antigens for antibody production. In a

most preferred embodiment, the mammalian cells do not express the laminin $\beta 2$ chain endogenously. In another preferred embodiment, the cells do not express all of the laminin 10 chains endogenously.

The protein may comprise additional sequences useful for promoting
5 purification of the protein, such as epitope tags and transport signals. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Manheim Biochemicals). Examples of such transport
10 signals include, but are not limited to, export signals, secretory signals, nuclear localization signals, and plasma membrane localization signals.

In one embodiment, at least one of the laminin chain polypeptide sequences, or fragments thereof, is operatively linked to a nucleic acid sequence encoding an “epitope tag”, so that at least one of the chains is expressed as a fusion protein with an
15 expressed epitope tag. The epitope tag may be expressed as the amino terminus, the carboxy terminus, or internal to any of the polypeptide chains comprising r-laminin 10, so long as the resulting r-laminin 10 remains functional.

In another embodiment, one of the r-laminin 10 chains is expressed as a fusion protein with a first epitope tag, and at least one other r-laminin chain is expressed as a fusion protein with a second epitope tag. This permits multiple rounds of purification
20 to be carried out. Alternatively, the same epitope tag can be used to create fusion proteins with more than one of the r-laminin chains.

In a further embodiment, the epitope tag can be engineered to be cleavable from the r-laminin 10 chain(s). Alternatively, no epitope tag is fused to any of the r-laminin 10 chains, and the r-laminin 10 is isolated by standard techniques, including
25 but not limited to affinity chromatography using laminin 10 specific antibodies or other laminin 10 binding molecules.

Media from cells transfected with a single laminin chain are initially analyzed on Western blots using laminin chain-specific antibodies. The expression of single laminin chains following transfection is generally intracellular. Clones showing
30 reactivity against individual transfected chain(s) are verified by any appropriate method, such as PCR, reverse transcription-PCR, or nucleic acid hybridization, to confirm incorporation of the transfected gene. Preferably, analysis of genomic DNA preparations from such clones is done by PCR using laminin chain-specific primer pairs. Media from transfected clones producing all three chains are further analyzed

for r-laminin 10 secretion and/or activity, by any appropriate method, including Western blot analysis and cell binding assays. Activity of the r-laminin 10 is preferably analyzed in a cell adhesion assay.

In a preferred embodiment, purification of r-laminin 10 is accomplished by
5 passing media from the transfected cells through an antibody affinity column. In one embodiment, antibodies against a peptide epitope expressed on at least one of the recombinant chains are attached to an affinity column, and bind the r-laminin 10 that has been secreted into the media. The r-laminin 10 is removed from the column by passing excess peptide over the column. Eluted fractions are analyzed by any
10 appropriate method, including gel electrophoresis and Western blot analysis. In a further embodiment, the peptide epitope can be cleaved after purification. In other embodiments, two or three separate r-laminin chains are expressed as fusion proteins, each with a different epitope tag, permitting two or three rounds of purification and a doubly or triply isolated r-laminin 10. The epitope tag can be engineered so as to be
15 cleavable from the r-laminin 10 chain(s) after purification. Alternatively, no epitope tag is fused to any of the r-laminin 10 chains, and the r-laminin 10 is isolated by standard techniques, including but not limited to affinity chromatography using laminin 10 specific antibodies or other laminin 10 binding molecules.

The laminin 10 polypeptide chains of the present invention also include (i)
20 substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more amino acid residues having substituents groups, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example,
25 polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of
30 charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340

(1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

The present invention further provides pharmaceutical compositions comprising isolated laminin 10 and a pharmaceutically acceptable carrier. In a preferred embodiment, the pharmaceutical composition comprises isolated r-laminin 10. According to this aspect of the invention, other agents can be included in the pharmaceutical compositions, depending on the condition being treated. The pharmaceutical composition may further comprise one or more other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, integrins, α -dystroglycan, entactin/nidogen, α -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or nerve growth factors, and peptide fragments thereof.

Pharmaceutical preparations comprising isolated laminin 10 can be prepared in any suitable form, and generally comprise the isolated laminin 10 in combination with any of the well known pharmaceutically acceptable carriers. The carriers can be injectable carriers, topical carriers, transdermal carriers, and the like. The preparation may advantageously be in a form for topical administration, such as an ointment, gel, cream, spray, dispersion, suspension or paste. The preparations may further advantageously include preservatives, antibacterials, antifungals, antioxidants, osmotic agents, and similar materials in composition and quantity as is conventional. Suitable solutions for use in accordance with the invention are sterile, are not harmful for the proposed application, and may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. For assistance in formulating the compositions of the present invention, one may refer to Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton, Pa. (1975).

In further aspect, the present invention provides methods and kits comprising isolated laminin 10, or pharmaceutical compositions thereof (and instructions for using the isolated laminin 10 in the kits) for accelerating the healing of injuries to vascular tissue, and for improving the biocompatibility of grafts used for treating such injuries. In a preferred embodiment of each of the methods disclosed below, isolated

laminin 10 is used. In specific examples, isolated laminin 10, isolated r-laminin 10, or pharmaceutical compositions thereof are used to:

- a. promote re-endothelialization at the site of vascular injuries;
- b. improve the "take" of grafts;
- 5 c. improve the biocompatibility of medical devices;
- d. promote cell attachment and subsequent cell stasis, proliferation, differentiation, and/or migration

by providing an amount effective of isolated laminin 10 or pharmaceutical compositions thereof for the various methods.

10 Endothelial cells normally rest on a subendothelium, composed of collagen type I/III, elastin, fibronectin, glycosaminoglycans, and a basement membrane, mainly consisting of laminin and type IV collagen. Several of the invasive treatments used in the repair of vascular occlusive diseases, or the disease itself, may cause large areas of endothelial cell-denudation in the vessel wall. Endothelialization is, in part,
15 dependent upon the underlying matrix, as subendothelial proteins have been shown to be important modulators of endothelial cell function (Madri, J.A. et al., *Am. J. Pathol.* 132(1), 18-27 (1988); and Madri, J.A. et al., *J. Cell Biochem.* 45(2), 123-30 (1991). In an effort to enhance endothelialization of grafts in humans, extensive research has been devoted to identifying substances that promote endothelial cell migration.
20 Endothelial cell migration is a key element of endothelialization of vascular grafts, whether by anastomotic ingrowth, transmural capillary ingrowth, adherence of circulating cells, or *ex vivo* cell seeding. Ultimately, it is desirable to encourage spontaneous migration *in vivo* because this would minimize the need for *ex vivo* graft and cell manipulation. In addition, retention of cells on the vascular surface is
25 necessary prior to migration (Dixit, P. et al., *J. Biomed. Mater. Res.* 56(4), 545-55 (2001)). Pretreatment of the graft with an adhesive substrate significantly enhances endothelial cell attachment to graft samples.

Laminin-8 and laminin-10 are secreted by endothelial cells, and are major components of the subendothelial basement membrane (Sorokin, L.M. et al., *Dev.*
30 *Biol.* 189(2), 285-300 (1997); Iivanainen, A. et al., *J. Biol. Chem.* 272(44), 27862-8 (1997); Patton, B. L. et al., *J. Cell Biol.* 139(6), 1507-21 (1997), Miner, J.H. et al., *J. Cell Biol.* 137(3), 685-701 (1997); Sorokin, L. et al., *Eur. J. Biochem.* 223(2), 603-10 (1994); and Tokida, Y. et al., *J. Biol. Chem.* 265(30), 18123-9 (1990)). The data

presented below demonstrates that isolated laminin 10 promotes endothelial cell attachment and migration.

Thus, in one embodiment the isolated laminin 10 is used to promote re-endothelialization, and to thus inhibit abnormal smooth muscle cell proliferation, at the site of a vascular injury. In another embodiment, isolated laminin 10 is coated
5 onto grafts to improve the “take” of grafts. As used herein the term “graft” refers to both natural and prosthetic grafts and implants.

In a further aspect, the present invention comprises medical devices with improved biocompatibility, wherein the devices are coated with isolated laminin 10 or
10 pharmaceutical compositions thereof, alone or in combination with other proteins or agents that serve to increase the biocompatibility of the device surface. The coated device stimulates cell attachment (such as endothelial cell attachment), and provides for diminished inflammation and/or infection at the site of entry of the appliance.

Such medical devices can be of any material used for implantation into the
15 body, and preferably are made of or coated with a biocompatible metal that may be either stainless steel or titanium. Alternatively, the device is made of or coated with a ceramic material, or a polymer including but not limited to polyester, polyglycolic acid or a polygalactose-polyglycolic acid copolymer.

One particular use of the present invention is to increase cell adhesion to
20 target surfaces, including but not limited to endothelial cell adhesion. For example, vascular grafts and stents may be coated with isolated laminin 10 or pharmaceutical compositions thereof to stimulate endothelial cell attachment.

If the device is made of a natural or synthetic biodegradable material in the form of a mesh, sheet or fabric, isolated laminin 10 or pharmaceutical compositions
25 thereof may be applied directly to the surface thereof. Appropriate cells may then be cultured on the matrix to form transplantable or implantable devices, including dental abutment pieces, needles, metal pins or rods, indwelling catheters, colostomy tubes, surgical meshes and any other appliance for which coating with isolated laminin 10 is desirable. Alternatively, the devices may be implanted and cells may be permitted to
30 attach in vivo.

Coupling of the isolated laminin 10 may be non-covalent (such as by adsorption), or by covalent means. The device may be immersed in, incubated in, or sprayed with the isolated laminin 10 or pharmaceutical compositions thereof.

The dosage regimen for various treatments using the isolated laminin 10 of the present invention is based on a variety of factors, including the type of injury or condition, the age, weight, sex, medical condition of the individual, the severity of the condition, and the route of administration. Thus, the dosage regimen may vary
5 widely, but can be determined routinely by a physician using standard methods. Laminins are extremely potent molecules, and one or a few molecules per cell could produce an effect. Thus, effective doses in the pico-gram per milliliter range are possible if the delivery is optimized. Laminins are sometimes present in an insoluble form in the basement membrane and have the capability of polymerizing at
10 concentrations as low as about 50 $\mu\text{g/ml}$, depending on the laminin isoform and the conditions. Laminins can also polymerize into a gel at a concentration of about 2-3 mg/ml. Dosage levels of the order of between 1 ng/ml and 10 mg/ml are thus useful for all methods disclosed herein, preferably between about 1 $\mu\text{g/ml}$ and about 3 mg/ml.

15 The present invention also provides a method for inducing cell attachment to the device (as disclosed above), comprising coating the appliance with isolated laminin 10 or pharmaceutical compositions thereof prior to incubation with cells appropriate for the desired application.

In another aspect of the present invention, isolated laminin 10 is used for the
20 culture of cells, including but not limited to endothelial cells, by contacting the cells with an amount effective of isolated laminin 10 to stimulate cell attachment and subsequent cell stasis, proliferation, differentiation, and/or migration. The isolated laminin 10 can either be provided in the cell culture medium, or as a cell culture medium supplement, or may be coated on the surface of a cell growth substrate. In a
25 preferred embodiment, the method further includes contacting the cells with other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, α -dystroglycan, cadherins, integrins, entactin/nidogen, α -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor or nerve growth factors, vascular endothelial growth factor,
30 fibroblast growth factor, and peptide fragments thereof.

The cells may comprise primary cells or cell culture cell lines. The methods of this aspect of the invention can be used in vivo, or in vitro.

In a preferred embodiment, isolated laminin 10 is used to coat the surface of a substrate, to promote cell adhesion to the substrate. The substrate used herein may be any desired substrate. For laboratory use, the substrate may be as simple as glass or plastic. For use in vivo, the substrate may be any biologically compatible material
5 capable of supporting cell adhesion. Suitable substrate materials include shaped articles made of or coated with such materials as collagen, regenerated collagen, polyglycolic acid, polygalactose, polylactic acid or derivatives thereof; biocompatible metals such as titanium and stainless steel; ceramic materials including prosthetic material such as hydroxylapatite; synthetic polymers including polyesters and nylons;
10 polystyrene; polyacrylates; polytetrafluoroethylene and virtually any other material to which biological molecules can readily adhere. The determination of the ability of a particular material to support adhesion of the isolated laminin 10 of the invention requires only routine experimentation by the skilled artisan.

In a further aspect, the present invention provides cell growth substrates for
15 adhesion and culturing of cells, by providing an amount effective of isolated laminin 10 for the attachment of cells to a cell culture device. The substrates may comprise any of the substrates discussed above.

In another aspect of the present invention, an improved cell culture medium is provided, wherein the improvement comprises addition to the cell culture medium of
20 an effective amount of isolated laminin 10 to the cell culture medium to promote the adherence, proliferation, and/or maintenance of cells. Any cell culture media that can support the growth of cells can be used with the present invention. Such cell culture media include, but are not limited to Basal Media Eagle, Dulbecco's Modified Eagle Medium, Iscove's Modified Dulbecco's Medium, McCoy's Medium, Minimum
25 Essential Medium, F-10 Nutrient Mixtures, Opti-MEM® Reduced-Serum Medium, RPMI Medium, and Macrophage-SFM Medium or combinations thereof.

The improved cell culture medium can be supplied in either a concentrated (ie: 10X) or non-concentrated form, and may be supplied as either a liquid, a powder, or a lyophilizate. The cell culture may be either chemically defined, or may contain a
30 serum supplement. Culture media is commercially available from many sources, such as GIBCO BRL (Gaithersburg, MD) and Sigma (St. Louis, MO). In an alternative embodiment, the laminin 10 is used as a cell culture supplement.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should

not be construed to limit the scope of the invention, as defined by the claims appended hereto.

Examples

5

Cloning of the Human Laminin α 5 cDNA

The previously published mouse laminin α 5 sequence (SEQ ID NO.:3) was used to search EST-databases. Based upon sequences of the identified ESTs, oligonucleotide primers were synthesized and used for PCR amplification of several human α 5 specific probes with λ gt11 cDNA library (Clontech) as template. These probes were used for screening of λ gt11 cDNA libraries (Clontech) from human lung, fetal lung and fetal kidney. This resulted in the isolation of several clones, and further screening was performed with PCR amplified selected regions of these clones. This walk generated clones covering 2134 base pair of coding sequence and 195 base pairs of 3'UTR in the C-terminal part, and 5354 base pairs in the N-terminal part, but lacking a translation initiation start site. The center part, comprising base pairs 5582-9316, was obtained by PCR amplification from a Human Lung MARATHON READY™ cDNA-mix (Clontech). The remaining 296 base pairs of coding sequence and a 67 base pair 5'UTR end was obtained with SMART™ RACE cDNA Amplification Kit (Clontech) using poly-A RNA purified with QuickPrep mRNA Purification Kit (Pharmacia Biotech) from HEK293 cell lysate. The reverse transcription was performed with the MMLV reverse transcriptase SuperscriptII (Life Technologies), and subsequent PCR amplification was performed with Advantage®-GC 2 PCR kit (Clontech). This 363 base pair N-terminal sequence was confirmed by sequencing genomic P1-clone (GenomeSystems) obtained by screening with a PCR generated probe from nucleotides 344-452. This generated a full-length sequence, but most of the sequence was only covered by a single λ -clone or PCR fragment. To further confirm the sequence, we used PCR amplification of SMART™RACE-generated cDNA-mixes from HEK293 cells, human placenta total RNA and from Human Lung Marathon Ready™ cDNA-mix. This generated new clones so that all regions of the cDNA were covered by more than one clone from different sources. In the case of suspected polymorphisms, several clones from different sources were compared. Sequencing was performed on an ABI PRISM™ 310 Genetic Analyzer

(Perkin Elmer) using ABI PRISM®BigDye™ Terminator Cycle Sequencing kit (PE Applied Biosystems). Sequence analysis was performed with AutoAssembler™ (PE Applied Biosystems) and sequence comparative analysis with the GCG-software (Group, G.C. et al., *Program for the GCG Package*, Version 10.1, Genetics Computer
5 Group, Madison, WI (2000)).

Expression Constructs

For expression of the human laminin $\alpha 5$ chain containing a C-terminal FLAG epitope, the full-length cDNA was constructed as follows. To obtain overlapping
10 cDNA clones, PCR amplification of SMART™ RACE-generated cDNA-mixes from HEK293 cells, human placenta total RNA, and Human Lung MARATHON READψ™ cDNA-mix was performed using ADVANTAGE®-GC 2 PCR kit and Pfu Turbo polymerase (Boeringer-Mannheim). All PCR derived cDNA fragments were cloned into the pCR2.1-TOPO vector (Invitrogen) and sequenced (AmpliTag FS on
15 an ABI310 sequencer, Perkin-Elmer) to ensure that no mutations had occurred during amplification. All primers for PCR and pCR2.1-TOPO™ plasmids into which the PCR derived cDNA fragments were cloned are shown in Table I. To ensure efficient and correct translation initiation, the Kozak sequence (accgcc, (Kozak, M., *J. Cell Biol.* 115(4), 997-903 (1991)) was edited to match the consensus. Primer KZK1
20 contained modified Kozak sequence and primer FLAG1 contained the FLAG sequence encoding the FLAG epitope (N-Asp-Tyr-Lys-Asp-Asp- Asp-Asp-Lys-C). (SEQ ID NO:37)

The EcoRI-BamHI insert from KBX3 was cloned into EcoRI-BamHI digested pUC18 vector to make KBX4. The BamHI-XbaI fragment from BBL3 was ligated
25 into BamHI-XbaI sites of KBX4 to make KBY1'. The BNK2' BclI-NotI fragment was cloned into KBY1' BclI-NotI sites to make KNX3. The 1.2 kilobase Bpu10I-NotI fragment of KNX3, which contained unwanted mutation was corrected by replacing the mutated fragment with non-mutated Bpu10I-NotI fragment from BNL12 to make KNX4'. The 1.8 kilobase BbvCI-SalI fragment of NSK5 was replaced by D29D30III
30 BbvCI-SalI fragment to make NSX1. The NotI-SalI fragment from NSX1 and AscI-EcoRI fragment containing FLAG epitope from SFK2 were cloned into SFL12 to make NFX4. The 5.3 kilobase NotI-HindIII fragment from NFX4 was ligated into NotI-HindIII sites of KNX4' to make KFX5 with full-length cDNA. The final

expression construct named HLN5Full.pcDNA was made by inserting the KFX5 EcoRI fragment into the EcoRI sites of pcDNA3.1/Zeo(-) mammalian expression vector (Invitrogen) in correct orientation. The construct used for expression of human laminin β 1 was constructed from a baculovirus expression vector (Pikkarainen, T. et al., *Eur. J. Biochem.* 209(2), 571-82 (1992)) by ligation of the insert into pIRES-
5 vector (Clontech). The construct used for expression of laminin γ 1 (HG1) has been described previously (Kortesmaa, J. et al., *J. Biol. Chem.* 275(20), 14853-9 (2000)).

Antibodies and Control Proteins

10 Anti-laminin α 5 (15H5, (Kikkawa, Y. et al., *J. Bio. Chem.* 273(25), 15854-9 (1998)) monoclonal antibody (mAb) was kindly provided by Dr. K. Sekiguchi. Anti-laminin β 1 (DG10, Virtanen, I. et al., *Am. J. Pathol.* 150(4), 1421-31 (1997)) mAb was kindly provided by Dr. I. Virtanen. Anti-laminin β 1 (2E8, Engvall, E. et al., *J. Cell Biol.* 103(6 Pt 1), 2457-65 (1986)) mAb was kindly provided by Dr. E. Engvall.
15 Anti-FLAG M2 mAb, purified control mouse IgG, collagen type I from calfskin, collagen type IV (Col IV) from mouse-EHS- tumor and heparin (grade I-A) were purchased from Sigma. Anti-laminin γ 1 (clone 22) mAb was purchased from Transduction Laboratories. Mouse mAb against integrin α 6 (BQ16) was purchased from Alexis Biochemicals. Mouse function blocking mAbs against integrin α 1
20 (FB12), α 2 (P1E6), α 3 (P1B5), α v (NKI-M9), α v β 3 (AM609), mouse mAb against integrin β 4 (ASC-3) and control rat IgG2a were obtained from Chemicon. Rat function blocking mAbs against integrin α 6 (GoH3), mouse function blocking mAbs against integrin β 1 (4B4) and mouse mAbs against integrin α 4 (HP2/1), α v (AMF-7), and β 3 (SZ-21) were obtained from Coulter. Secondary Ab conjugates anti-mouse
25 IgG-horseradish peroxidase (HRP) and FITC-conjugated F(ab)2 fragments of rabbit anti-mouse immunoglobulin were purchased from Dako. RGDS-peptide, cyclical RGDS-peptide, control RAGS-peptide, mouse mAb against integrin α 5 (P1D6) and human vitronectin from plasma were purchased from Life Technologies. Human fibronectin (FN) from plasma was obtained from Roche. EHS-derived laminin-
30 1/nidogen complex (laminin-1/Nd) was kindly provided by Dr. J. Engel.

Production and Purification of Recombinant Laminin-10

r-laminin-10 was produced in human embryonic kidney cells (HEK293, ATCC CRL-1573) cultured in DMEM, pyruvate, 10% FCS in humidified 5% CO₂ atmosphere at 37°C. Wild-type cells were transfected using the standard calcium-phosphate method with the HG1 construct and stable colonies were selected using 100 mg/ml hygromycin (Cayla). All further cell culture and clonal expansion was carried out in continuous presence of relevant selection antibiotics. A highly expressing clone was then transfected with the human laminin β 1 construct and stable clones were selected using 500 mg/ml G418 (Life Technologies). A clone highly expressing both laminin γ 1 and laminin β 1 was finally transfected with HLN5Full.pcDNA and stable colonies were selected using 200 mg/ml zeocin (Cayla). The clones showing the highest secretion were expanded further.

For production of r-laminin-10, confluent cells were cultured in DMEM supplemented with 1mM pyruvate and insulin-transferrin-selen supplement (Sigma) for up to five days. r-laminin-10 was affinity purified using anti-FLAG M2 matrix (Sigma). The collected medium was incubated in batch mode with the matrix overnight at 4°C with agitation. Bound r-laminin-10 was competitively eluted with 50 mg/ml FLAG peptide (Sigma) in TBS/E (50 mM Tris-Cl, pH 7.5, 150 mM NaCl, 1 mM EDTA) at room temperature. The elute was concentrated and the buffer was replaced by PBS using 30 kD cut-off ultrafiltration (Millipore). Finally the concentrated solution was passed through 0.2 mm filter to remove self-aggregated polymers. Recombinant human laminin-8 (r-laminin -8) was produced in HEK293 cells and isolated using anti-FLAG matrix and ion-exchange chromatography.

25 Characterization of Recombinant Laminin-10

Secreted laminin in medium and after purification was characterized using 5% SDS-PAGE and 4-15% gradient SDS-PAGE. Proteins were visualized using silver staining or transferred onto PVDF. The membranes were probed with mAbs described above. After washing, the membranes were incubated with HRP-conjugated goat anti-mouse antibody. The immunoreactivity was detected by a chemiluminescent kit (Life Science Products) according to the manufacturer's instructions.

Electron microscopy was performed by the rotary shadowing technique as described previously (Engel, J., Methods Enzymol. 245, 469-88 (1994)). Briefly,

protein (25-50 mg/ml) in 0.2 M ammonium bicarbonate, pH 7.4, or 0.1 M acetic acid was mixed with an equal volume of glycerol and sprayed onto freshly cleaved mica discs. These were dried in high vacuum, shadowed with platinum/carbon at an angle of 9° and replicated. Negative staining was performed at neutral pH in order to avoid dissociation of aggregates by the acid pH in the routine procedure. Ten ml of a solution in PBS was put on a glow discharged collodium and carbon grid and 5 ml of a 2% sodium phosphotungstate solution of pH 7 was added. After removal of the first stain, incubation was repeated for 2 min.

10 *Cell Culture and HSVEC isolation*

Human fibrosarcoma HT-1080 (CCL-121) cells were from ATCC. Immortomouse brain capillary endothelial (Kanda, S. et al Exp. Cell Res. 248(1), 203-13 (1999)) cells were kindly provided by Dr. L. Claesson-Welsh. All cells were cultured in humidified 5% CO₂ atmosphere. HT-1080 cells were cultured in DMEM, 10% FCS, pyruvate at 37°C. IBE cells were cultured in F-12, 10% FCS, 2 units/ml γ -interferon on gelatin-coated plastic at 33°C. Prior to assay, the IBE cells were cultured in serum-free F-12 at 37°C without γ -interferon for 24 hours.

As approved by the ethical committee at the Karolinska Hospital, Stockholm, Sweden, residual segments of the great saphenous vein were collected from patients undergoing coronary bypass surgery. HSVECs were isolated as previously described (Haegerstrand, A. et al., J. Vasc. Surg. 16(2), 280-5 (1992)). Briefly, veins were rinsed with MEM (Life Technologies) and filled with 0.1% collagenase and 0.16% dispase (Boehringer Mannheim) in MEM for 20 min at 37°C in an 8% CO₂-humidified atmosphere. Cells were cultured in MEM containing 40% heat-inactivated pooled human serum (HS), 1 nmol/L cholera toxin (CT; Sigma), 33 mmol/L isobutylmethylxantine (IBMX; Sigma), and antibiotics. HSVECs were seeded on gelatin-coated plates and passaged (1:3). HSVECs were characterized with monoclonal anti-human von Willebrand factor-related antigen (Dako) and HSVECs between passages 4 and 7 were used in the experiments.

30

Cell Adhesion Assays

Adhesion assay was performed as described previously (Kortesmaa, J. et al., J. Biol. Chem. 275(20), 14853-9 (2000)). Briefly, 96-well plates (Maxi-Sorp, Nunc)

were coated with proteins overnight at 4°C. The remaining protein binding capacity was saturated by addition of 2% heat-inactivated BSA in PBS.

For the assay, cells were suspended in buffered serum-free medium at 3×10^4 cells/well. DMEM, 25mM Hepes, pyruvate was used for HT-1080 cells, F-12, 25 mM Hepes, 0.25% BSA for others. Antibodies or other test compounds were added to the cell suspension and the cells were allowed to recover at 37°C for 30 min. Integrin mAbs were used at 10 mg/ml, RGD-peptides at 0.25 mg/ml, heparin at 5 mg/ml, and EDTA at 5mM. The cells were then allowed to adhere for 60 min at 37°C. Bound cells were quantitated by crystal violet staining. None of the cell lines bound appreciably to BSA. When the quantitative results were calculated, binding to BSA was given a value of zero, while the relevant control was given the value 100. The mean and standard deviation (S.D.) were calculated from results obtained from parallel wells.

15 *Immunofluorescence Flow Cytometry*

Briefly, suspended HSVECs were incubated in PBS containing anti-integrin mAbs against $\alpha 1-6$, αv , $\beta 1$, $\beta 3$, and $\beta 4$ for 30 min at 4°C. Following washing, cells were incubated with FITC-conjugated F(ab)₂ fragments of rabbit anti-mouse immunoglobulin for 30 min at 4°C. Cells were then analyzed in a FACS can flow cytometer (Becton Dickinson). Mouse IgG was used as a negative control.

Cell Migration Assays

Cell migration assay was performed as described previously (Jansson, K. et al., Eur. J. Vasc. Endovasc. Surg. 16(4), 334-41 (1998)). Flat-bottom 24-well culture plates (Corning) were coated with proteins overnight at 4°C. The remaining protein binding capacity was saturated by addition of 2% heat-inactivated BSA in PBS. Thereafter a 4x10 mm stainless steel-weight was put on the center of well, before seeding HSVECs at 2×10^5 cells/well. After adhesion for 2 days in MEM with 30% HS, the steel-weight was removed. A gap devoid of HSVECs was thus created, with two broad (10 mm) EC-edges facing each other at a distance of 4 mm. During endothelialization, HSVECs were incubated in MEM with 40% HS, CT and IBMX for 2 days after removing the steel-weight. The cells were visualized by 0.1% crystal violet staining.

Results

Sequence of Human Laminin Alpha 5 Chain

The full-length laminin $\alpha 5$ cDNA coding sequence (Fig. 1) (SEQ ID NO:1) consisted of 11,088 base pair with an open reading frame encoding 3696 amino acids (SEQ ID NO.:2). Compared to the previously reported mouse laminin $\alpha 5$ sequence (GENBANK™ accession number U37501; Miner, J.H. et al., J. Biol. Chem. 270(48), 28523-6 (1995)) (SEQ ID NO.:4), we obtained an additional 79 amino acids in the N-terminal end. The mouse sequence has an additional stretch of 20 amino acids in the C-terminus, compared to the human sequence. Alignment of mouse and human laminin LG5-modules with other published sequences (not shown) revealed similar C-terminal length in all cases except for the mouse $\alpha 5$. Comparison with the mouse laminin $\alpha 5$ showed an overall amino-acid identity of 79%. The previously reported adhesive tripeptide sequence LRE (Hunter, D.D. et al., Cell 59(5), 905-13 (1989)) was not conserved in the human chain (amino acid residues; 3176-3178 LQQ), while the two RGD-sequences were conserved (Fig. 1). The human sequence contained two extra cysteines (amino acid residues; 3173 and 3663) and a hinge region between LG 3 and LG 4 that is seven residues longer than the mouse sequence. In addition, there was a stretch of four extra amino acids in domain IV (amino acid residues; 1680-1683) in the human sequence. We generated cDNAs from four different sources (placenta, HEK293 cells, and lung-marathon-ready-cDNA from two sources) and thereby detected four possible polymorphisms in domain IIIa; 5698:A-G (1900: Met-Val), 5722: G-A (1908: Ala-Thr), 6158: G-A (2053: Arg-Thr), 6184: A-G (2062: Asn-Asp) and one in the G domain; 9235:T-C (3079: Trp-Arg). The amino acids chosen for the r-laminin-10 construct at these possible polymorphic sites are those shown in Fig. 1.

Production and Characterization of Recombinant laminin-10

Conditioned medium from wild-type HEK293 cells did not react in western blotting with the anti-laminin $\alpha 5$, anti-laminin $\beta 1$, anti-laminin $\gamma 1$, or anti-FLAG Abs, indicating that these cells express endogenous laminins at very low amounts if at all (data not shown). After triple transfection, the best cell clone produced 2-3 mg of r-laminin-10 per liter of medium, which is quite high considering the size and complexity of the protein.

Immunoaffinity purification with anti-FLAG M2 matrix followed by competitive elution with FLAG-peptide resulted in highly purified protein as seen in silver stained SDS-PAGE gels (Fig 2a). Under reducing conditions, two bands were seen, a 400 kD band corresponding to the laminin $\alpha 5$ chain and a 200 kD band
5 corresponding to the laminin $\beta 1$ and $\gamma 1$ chains, which have similar molecular weights (Fig. 2a). In western blotting of the conditioned medium, two bands of approximately 350 and 400 kD could be seen with the laminin $\alpha 5$ mAb (Fig. 2b). The anti-FLAG antibody reacted with a 400 kD and a 40 kD fragment (Fig 2b and not shown). Taken together, these data indicate that the 400 kD fragment is the intact laminin $\alpha 5$, the 350
10 kD is a N-terminal fragment and the 40 kD is a C-terminal fragment harboring the FLAG epitope. Under non-reducing conditions, most of the protein appeared at the top of the gel as a very high molecular weight band, which was immunoreactive with $\alpha 5$, FLAG, $\beta 1$ and $\gamma 1$ mAbs, showing that the r-laminin-10 was produced as disulfide-crosslinked heterotrimer (Fig. 2c). A minor band of approximately 400 kD was also
15 seen in silver staining and in western blotting with $\alpha 5$, FLAG, $\beta 1$ and $\gamma 1$ mAbs. The non-covalently associated $\alpha 5$ chain had an apparent molecular weight similar to the $\beta 1/\gamma 1$ dimer, which explains the immunoreactivity of the minor band with $\alpha 5$ and FLAG mAbs.

Rotary shadowing EM revealed the r-laminin-10 protein as having three short
20 arms and one long arm in accordance with the expected structure. Some monomers were shown to have an elongated globular domain in one of the short arms, which could be domain IVb. Oligomers dominated the preparation.

Cell Binding to r-laminin-10

25 Vascular endothelial cells undergo drastic morphological and functional changes during angiogenesis, and it is well established that the behavior of the cell is critically influenced by its interaction with components of the extracellular matrix. Because of this fact, endothelial cell attachment and migration on grafts used in vascular surgery
30 might be improved if the surfaces of these non-biological materials would be pre-coated with ECM proteins, e. g. laminins. The ingrowth of endothelial cells on the surfaces of grafts, a process known as endothelialization, has been shown to be of critical importance for preventing thrombus formation on the graft material, and for reducing neointimal hyperplasia. Many adhesive substrate coatings to enhance

endothelial cell attachment have been tested (Dixit, P., et al. (2001) *J. Biomed. Mater. Res.* 56(4), 545-55), but the long term patency of small-diameter vascular grafts is still disappointing, primarily due to stenosis and thrombus formation (Pevec, W. C., et al. (1992) *J. Vasc. Surg.* 16(1), 60-5; Watelet, J., et al. (1997) *Ann. Vasc. Surg.* 11(5), 510-9).

To investigate the biological activity of r-laminin-10, we assayed it for cell adhesion properties. Cell adhesion onto the laminin coated substratum is mediated predominantly by the integrin family of adhesion receptors. Several integrins have been implicated as receptors for laminin-10 or laminin-10/ 11, including $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 1$, and $\alpha 6\beta 4$ (Kikkawa, Y. et al., *J. Biol. Chem.* 273(25), 15854-9 (1998); Kikkawa, Y. et al., *J. Cell Sci.* 113(Pt 5), 869-76 (2000); Ferletta, M. et al., *J. Cell Sci.* 112 (Pt 1), 1-10 (1999); Gu, Y. et al., *Blood* 93(8), 2533-42 (1999); Pouliot, N. et al., *Exp. Cell Res.* 261(2), 360-71 (2000); and Tani, T. et al., *Exp. Cell Res.* 248(1), 115-21 (1999)). In addition, Nielsen and co-workers recently demonstrated that domain IV of the laminin $\alpha 5$ chain is a binding site for integrin $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 4\beta 1$, and $\alpha 6\beta 1$ (Nielsen, P.K. et al., *J. Biol. Chem.* 276(14), 10906-12 (2001)). As a general model, we used the HT-1080 fibrosarcoma cell line, which expresses a wide variety of integrin receptors such as $\alpha 2$, $\alpha 3$, $\alpha 5$, $\alpha 6$ and $\beta 1$ (Wayner, E.A. et al., *J. Cell Biol.* 121(5), 1141-52 (1993)). Different blocking anti-integrin antibodies were used to identify the integrin receptors mediating cell binding to r-laminin-10. Two endothelial cell types were also studied: HSVECs were used as model for macrovascular endothelial cells and IBE cells for microvascular endothelial cells. HT-1080 cells adhered to fibronectin equally strongly as to r-laminin-10 (Fig. 3a) while laminin-1 and r-laminin-8 were less effective in promoting cell adhesion (Fig. 3a). Similar results were obtained with IBE cells and HSVECs (Fig. 3b and c). Based on these results, further experiments with blocking integrin mAbs were performed using a coating concentration of 10 mg/ml.

Monoclonal Abs against either $\alpha 3$ or $\beta 1$ inhibited HT-1080 cell binding to r-laminin-10 by approximately 80%, indicating that integrin $\alpha 3\beta 1$ was a major mediator of adhesion to r-laminin-10 (Fig. 4). In addition, mAbs against integrin $\alpha 2$ had partial inhibitory effect on adhesion to r-laminin-10 (Fig. 4). Since some adhesion remained after blocking of the integrin $\beta 1$, other receptor classes besides $\beta 1$ could be involved in the cell adhesion. Monoclonal Abs against integrins $\alpha 6$ and αv had no effects on the

adhesion of HT-1080 cells to r-laminin-10 either alone (Fig. 4) or in various combinations ($\alpha 3 + \alpha 6$, $\beta 1 + \alpha 6$, $\beta 1 + \alpha v \beta 3$, $\beta 1 + \alpha 6 + \alpha v \beta 3$, $\beta 1 + \alpha 6 + \alpha v$; not shown). This indicates that $\alpha 6$ integrins ($\alpha 6 \beta 1$, $\alpha 6 \beta 4$) or αv integrins ($\alpha v \beta 1$, $\alpha v \beta 3$ or $\alpha v \beta 5$) were not mediating the cell adhesion.

5 HSVEC binding to the r-laminin-10 was also studied. To determine which integrins were present on the cell surface, we performed fluorescent cell sorting assay using mAbs against integrin subunits $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$, αv , $\beta 1$, $\beta 3$ and $\beta 4$. From these results it can be concluded that HSVEC express large amounts of $\alpha 2 \beta 1$, $\alpha 5 \beta 1$ and $\alpha v \beta 3$, moderate amounts of $\alpha 3 \beta 1$, and small amounts of $\alpha 1 \beta 1$, $\alpha 6 \beta 1$ and $\alpha 6 \beta 4$, but
10 integrin $\alpha 4 \beta 1$ was not detected. The HSVEC binding was most efficiently inhibited by mAbs against integrin $\alpha 3$ and $\beta 1$, but also against $\alpha 2$ (Fig. 3) had partial effect, in a fashion similar to that observed for HT-1080 cells. Integrin $\alpha 6$ was only weakly expressed on HSVECs and, consequently, mAbs against this integrin did not inhibit binding to r-laminin-10.

15 Cell adhesion to r-laminin-10 was found to be dependent of divalent cations since it could be abolished by 5 mM EDTA in both HT-1080 cells and HSVECs (Fig.3). Heparin, when used at 5 mg/ml, had no effect on the adhesion of either cell type (Fig. 3). Since the $\alpha 5$ -chain has conserved RGD-sequences, we tested the effect of RGD peptides, which are reported to block the function of various RGD-dependent
20 integrins (such as $\alpha 5 \beta 1$ and the αv family) (Pierschbacher, M.D. et al., Nature 309(5963), 30-3 (1984)). Neither linear nor cyclic RGD-peptides had any effect at 0.25 mg/ml concentration on adhesion of either HT-1080 cells or HSVECs to r-laminin-10 (Fig. 4). It was, furthermore, observed that the cell binding activity of r-laminin-10 was sensitive to air-drying, as we have previously reported for r-laminin-8
25 (Kortessmaa, J. et al., J. Biol. Chem. 275(20), 14853-9 (2000)). When the coated protein was allowed to air dry for 20 min at room temperature before adding the cells, the cell binding activity of r-laminin-10 was completely lost (data not shown).

Cell Migration

30 Laminins have been shown to stimulate cell migration during development, and in many pathological processes. We examined the ability to promote HSVEC migration on dishes coated with 10 mg/ml of r-laminin-10 or other adhesive proteins. The migration assay was repeated three times using HSVEC obtained from three

different donors. Among the seven different adhesive proteins examined, r-laminin-10 was the most potent in promoting HSVEC migration *in vitro*. In addition to r-laminin-10, type IV collagen was also quite potent in promoting HSVEC migration. Laminin N-1 and gelatin were of roughly equal potency but significantly lower than r-laminin-10, and r-laminin-8 was the least potent among the proteins examined.

Discussion

Several cell types have been tested for identification of the integrin receptors for laminin-10, but no report exists concerning endothelial cells. In this study, we demonstrated that HSVECs use integrins $\alpha 2\beta 1$ and $\alpha 3\beta 1$ to mediate cell adhesion to r laminin-10, and similar results were obtained for HT-1080 cells. An antibody against the integrin $\alpha 6$ subunit, either alone or combination with other mAbs ($\alpha 3+\alpha 6$, $\beta 1+\alpha 6$, $\beta 1+\alpha 6+\alpha v\beta 3$, $\beta 1+\alpha 6+\alpha v$), did not inhibit cell adhesion (Fig.4 and not shown), indicating that integrin $\alpha 6$ is not an important receptor in these cells for r laminin-10, although the $\alpha 6$ integrins have previously been implicated as receptors for laminins in general and laminin-10 in particular (Kikkawa, Y. et al., J. Cell Sci. 113(Pt 5), 869-76 (2000)).

HSVECs, as well as HT-1080 and IBE cells, attached to r-10 more strongly than to laminin-1 and r laminin-8. Poor adhesion of HSVECs to r laminin-8 is not surprising considering the fluorescent cell sorting data showing that the cells have little $\alpha 6$ integrins, which have previously been shown to be receptors for r-laminin-8 (Kortesmaa, J. et al., J. Biol. Chem. 275(20), 14853-9 (2000)). We can, therefore, conclude that the integrin-binding is distinctly different between the two main forms of endothelial laminins, as well as between different endothelial cell types, as we have previously shown that IBE and bovine capillary endothelial cell adhesion onto r-laminin-8 is mediated predominantly by $\alpha 6$ integrins (Kortesmaa, J. et al., J. Biol. Chem. 275(20), 14853-9 (2000)).

Cell migration-promoting activities of different laminins appear to be dependent on cell specific factors. Human glioblastoma cell line T98G showed best migration on laminin-8 (Fujiwara, H. et al., J. Biol. Chem. 276(20), 17550-8 (2001)) compared to laminin-2/4, laminin-5, laminin-10/11 and fibronectin, while LIM1215 carcinoma cells migrate more efficiently on laminin-10 than on collagen type I, type IV or laminin-1 (Pouliot, N. et al., Exp. Cell Res. 266(1), 1-10 (2001)). Here, we

demonstrated that r-laminin 10 was the most potent matrix of the components tested in promoting endothelial cell (HSVEC) migration *in vitro* (Fig. 5). Interestingly, HSVEC adhesion to commercial laminin-10/11 and to r-laminin-10 was equally strong, but the potency of laminin-10/11 in promoting HSVEC migration was much
5 lower than that of r-laminin-10.

We claim:

1. An isolated nucleic acid consisting of a sequence that encodes a polypeptide
5 with the amino acid sequence of SEQ ID NO:2.
2. The isolated nucleic acid of claim 1 wherein the nucleic acid consists of the
sequence of SEQ ID NO:1.
- 10 3. A recombinant expression vector comprising the isolated nucleic acid
sequence of claim 1 operatively linked to a promoter.
4. A host cell transfected with the recombinant expression vector of claim 3.
- 15 5. An isolated laminin α 5 polypeptide, consisting of the amino acid sequence of
SEQ ID NO:2.
6. Isolated laminin 10.
- 20 7. The isolated laminin 10 of claim 6, wherein the isolated laminin 10 is
recombinant laminin 10.
8. The isolated recombinant laminin 10 of claim 7 comprising:
a first chain encoded by a polynucleotide that hybridizes under high stringency
25 conditions to a coding region of one or more sequence selected from the group
consisting of SEQ ID NO:1 and SEQ ID NO:3;
a second chain encoded by a polynucleotide that hybridizes under high
stringency conditions to a coding region of one or more sequence selected from the
group consisting of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, and SEQ ID
30 NO:11; and
a third chain encoded by a polynucleotide that hybridizes under high
stringency conditions to a coding region of one or more sequence selected from the
group consisting of SEQ ID NO: 13, SEQ ID NO:15, SEQ ID NO:17, and SEQ ID
NO:19;

wherein the first, second, and third chains are assembled into recombinant laminin 10.

9. The isolated recombinant laminin 10 of claim 7 comprising:

5 a first chain comprising a polypeptide at least 70% identical to one or more polypeptide sequences selected from the group consisting of SEQ ID NO:2, and SEQ ID NO:4;

a second chain comprising a polypeptide at least 70% identical to one or more polypeptide sequences selected from the group consisting of SEQ ID NO:6, SEQ ID
10 NO:8, SEQ ID NO:10, and SEQ ID NO:12; and

a third chain comprising a polypeptide at least 70% identical to one or more polypeptide sequences selected from the group consisting of SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, and SEQ ID NO:20;

15 wherein the first, second, and third chains are assembled into recombinant laminin 10.

10. The isolated recombinant laminin 10 of claim 7 comprising a first, second, and third polypeptide chain, wherein the first, second, and third polypeptide chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R3; (2)
20 R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is an amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted
25 protein, or it may be an artificial sequence; R3 is a secreted α 5 laminin chain for the first polypeptide chain, a secreted β 1 laminin chain for the second polypeptide chain, and a secreted γ 1 laminin chain for the third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag.

30 11. Recombinant laminin 10-expressing host cells.

12. The recombinant laminin 10-expressing host cells of claim 11, wherein the recombinant laminin 10 comprises:

a first chain encoded by a polynucleotide that hybridizes under high stringency conditions to a coding region of one or more sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3;

5 a second chain encoded by a polynucleotide that hybridizes under high stringency conditions to a coding region of one or more sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, and SEQ ID NO:11; and

10 a third chain encoded by a polynucleotide that hybridizes under high stringency conditions to a coding region of one or more sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO:15, SEQ ID NO:17, and SEQ ID NO:19;

wherein the first, second, and third chains are assembled into recombinant laminin 10.

15 13. The isolated recombinant laminin 10-expressing host cells of claim 11, wherein the recombinant laminin 10 comprises:

a first chain comprising a polypeptide at least 70% identical to one or more polypeptide sequences selected from the group consisting of SEQ ID NO:2, and SEQ ID NO:4;

20 a second chain comprising a polypeptide at least 70% identical to one or more polypeptide sequences selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, and SEQ ID NO:12; and

25 a third chain comprising a polypeptide at least 70% identical to one or more polypeptide sequences selected from the group consisting of SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, and SEQ ID NO:20;

wherein the first, second, and third chains are assembled into recombinant laminin 10.

30 14. The host cells of claim 11, wherein the host cell is a mammalian cell.

15. The host cells of claim 13, wherein at least one of the first, second, or third chains is expressed as a fusion protein with an epitope tag.

16. A method of isolating recombinant laminin 10, comprising:

- a. providing the host cells of claim 13;
 - b. growing the cells in cell culture medium under conditions to stimulate expression of the recombinant laminin 10 chains;
 - c. passing the cell culture medium through an affinity chromatography column, wherein the column contains a compound that binds to the recombinant laminin 10;
 - d. washing the affinity column to remove unbound materials; and
 - e. eluting the bound recombinant laminin 10 from the column.
- 10 17. Isolated recombinant laminin 10 isolated according to the method of claim 16.
18. A method to improve the biocompatibility of a medical device or graft, comprising contacting the medical device or graft with an amount effective of isolated laminin 10 to improve the biocompatibility of the medical device or graft.
- 15 19. An improved medical device or graft, wherein the improvement consists of providing a medical device or graft with an amount effective of isolated laminin 10 to improve the biocompatibility of the medical device or graft.
- 20 20. A method to promote cell adhesion and/or cell migration to a surface, comprising contacting cells with an amount effective of isolated laminin 10 to promote cell adhesion and/or cell migration to the surface.
21. An improved cell growth substrate, wherein the improvement consists of providing a cell growth substrate that has been coated with an amount effective of laminin 10 to promote cell attachment to the cell growth substrate.
- 25 22. A method to accelerate healing of a vascular tissue injury in a subject, comprising contacting the site of the vascular tissue injury of the subject with an amount effective of laminin 10 to promote re-endothelialization at the vascular tissue injury site.
- 30 23. A pharmaceutical composition comprising:
 - a) the isolated laminin 10 of claim 6; and

- b) a pharmaceutically acceptable carrier.

Fig. 1

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Fig. 2

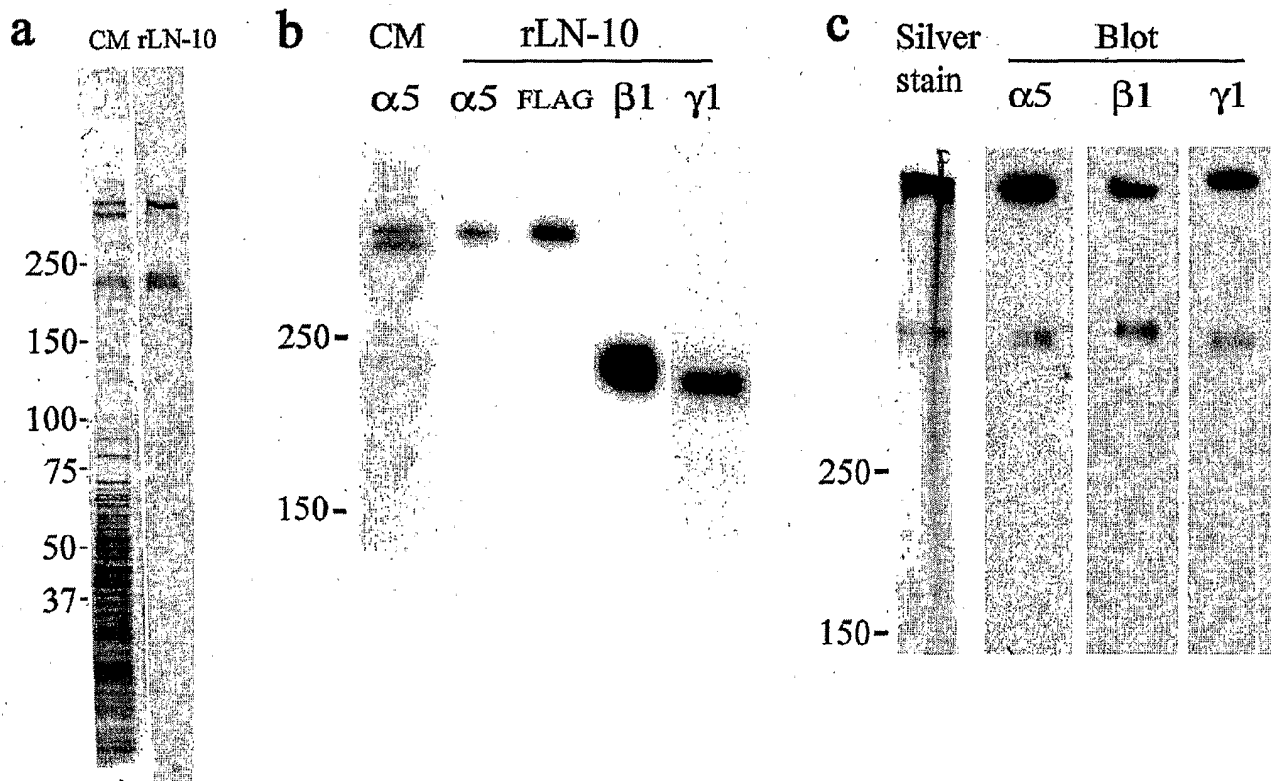


Fig. 43

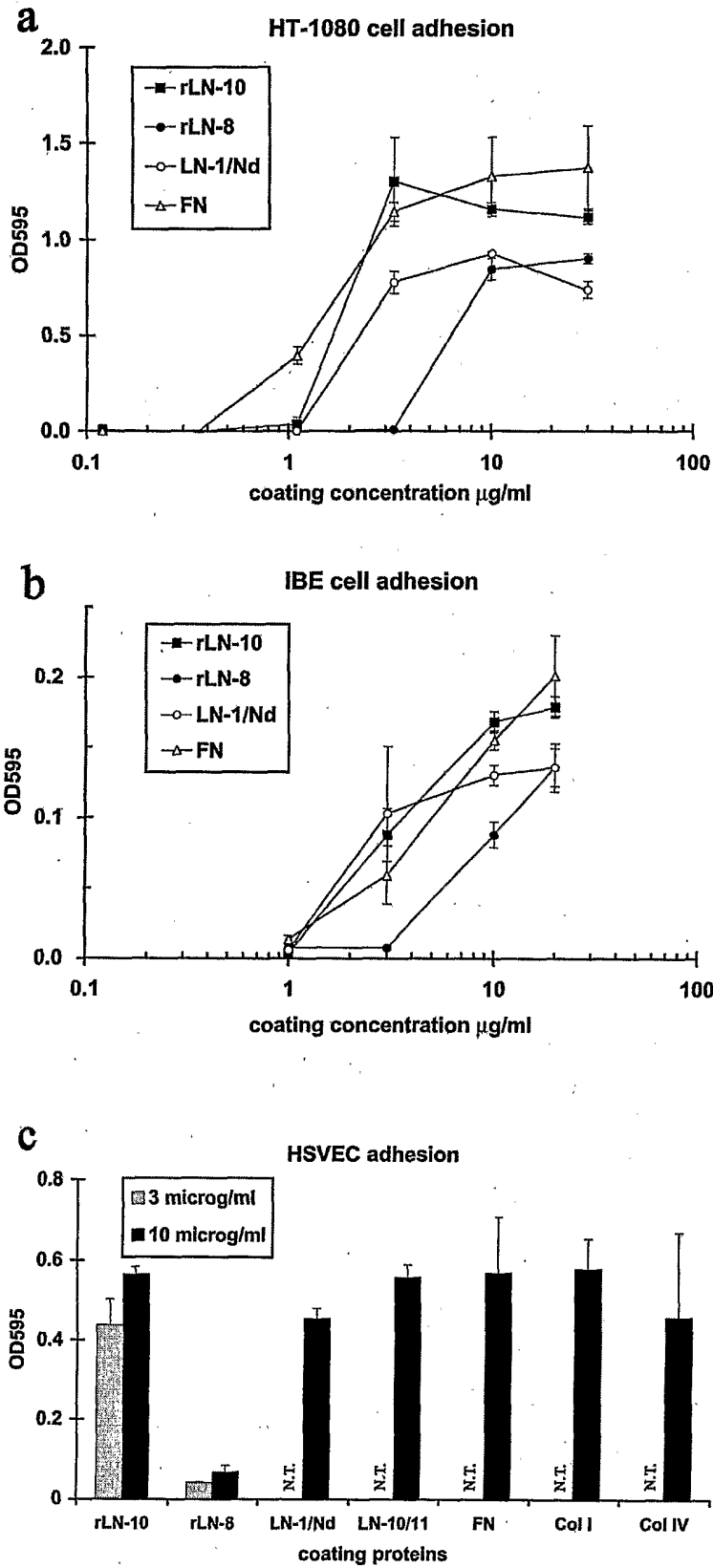
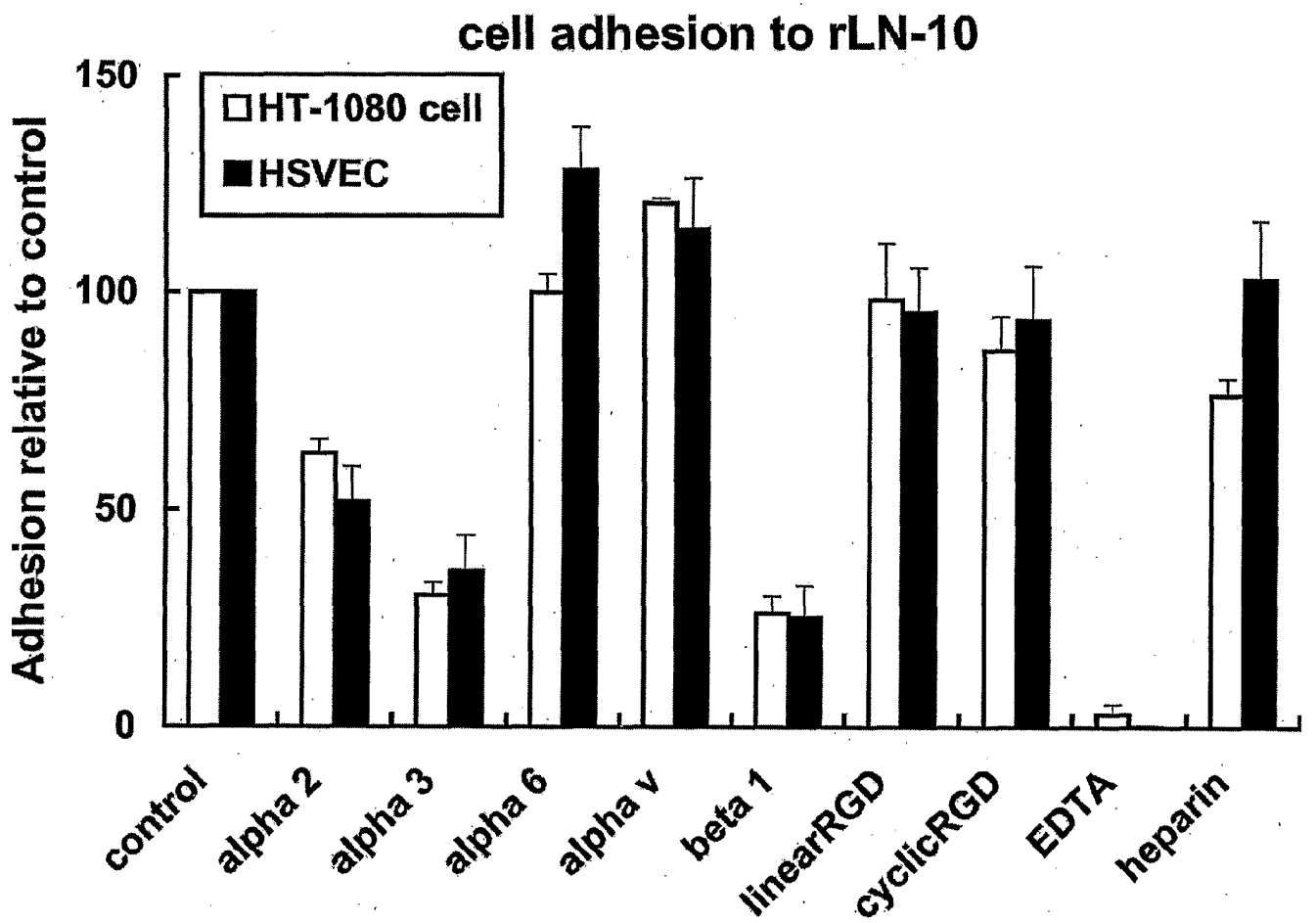
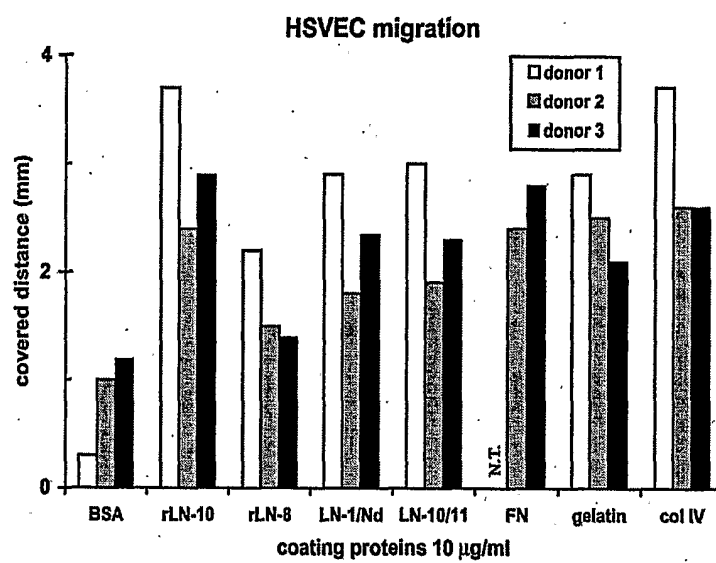


Fig. 6⁴



5



SEQUENCE LISTING

<110> Tryggvason, Karl
Doi, Masayuki
Thyboll, Jill

<120> Recombinant Laminin 10

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atc aag ttt gcc aac tca ccc cgg ccg gac ctc tgg gtg ctg gag cgg Ile Lys Phe Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg 160 165 170			589
tcc atg gac ttc ggc cgc acc tac cag ccc tgg cag ttc ttt gcc tcc Ser Met Asp Phe Gly Arg Thr Tyr Gln Pro Trp Gln Phe Phe Ala Ser 175 180 185 190			637
tct aag agg gac tgt ctg gag cgg ttc ggg cca cag acg ctg gag cgc Ser Lys Arg Asp Cys Leu Glu Arg Phe Gly Pro Gln Thr Leu Glu Arg 195 200 205			685
atc aca cgg gac gac gca gcc atc tgc acc acc gag tac tca cgc atc Ile Thr Arg Asp Asp Ala Ala Ile Cys Thr Thr Glu Tyr Ser Arg Ile 210 215 220			733
gtg ccc ctg gag aac gga gag atc gtg gtg tcc ctg gtg aac gga cgt Val Pro Leu Glu Asn Gly Glu Ile Val Val Ser Leu Val Asn Gly Arg 225 230 235			781
ccg ggc gcc atg aat ttc tcc tac tcg ccg ctg cta cgt gag ttc acc Pro Gly Ala Met Asn Phe Ser Tyr Ser Pro Leu Leu Arg Glu Phe Thr 240 245 250			829
aag gcc acc aac gtc cgc ctg cgc ttc ctg cgt acc aac acg ctg ctg Lys Ala Thr Asn Val Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu 255 260 265 270			877
ggc cat ctc atg ggg aag gcg ctg cgg gac ccc acg gtc acc cgc cgg Gly His Leu Met Gly Lys Ala Leu Arg Asp Pro Thr Val Thr Arg Arg 275 280 285			925
tat tat tac agc atc aag gat atc agc atc gga ggc cgc tgt gtc tgc Tyr Tyr Tyr Ser Ile Lys Asp Ile Ser Ile Gly Gly Arg Cys Val Cys 290 295 300			973
cac ggc cac gcg gat gcc tgc gat gcc aaa gac ccc acg gac ccg ttc His Gly His Ala Asp Ala Cys Asp Ala Lys Asp Pro Thr Asp Pro Phe 305 310 315			1021
agg ctg cag tgc acc tgc cag cac aac acc tgc ggg ggc acc tgc gac Arg Leu Gln Cys Thr Cys Gln His Asn Thr Cys Gly Gly Thr Cys Asp 320 325 330			1069

cgc tgc tgc ccc ggc ttc aat cag cag ccg tgg aag cct gcg act gcc	1117
Arg Cys Cys Pro Gly Phe Asn Gln Gln Pro Trp Lys Pro Ala Thr Ala	
335 340 345 350	
aac agt gcc aac gag tgc cag tcc tgt aac tgc tac ggc cat gcc acc	1165
Asn Ser Ala Asn Glu Cys Gln Ser Cys Asn Cys Tyr Gly His Ala Thr	
355 360 365	
gac tgt tac tac gac cct gag gtg gac cgg cgc cgc gcc agc cag agc	1213
Asp Cys Tyr Tyr Asp Pro Glu Val Asp Arg Arg Arg Ala Ser Gln Ser	
370 375 380	
ctg gat ggc acc tat cag ggt ggg ggt gtc tgt atc gac tgc cag cac	1261
Leu Asp Gly Thr Tyr Gln Gly Gly Val Cys Ile Asp Cys Gln His	
385 390 395	
cac acc gcc ggc gtc aac tgt gag cgc tgc ctg ccc ggc ttc tac cgc	1309
His Thr Ala Gly Val Asn Cys Glu Arg Cys Leu Pro Gly Phe Tyr Arg	
400 405 410	
tct ccc aac cac cct ctg gac tgc ccc cac gtc tgc cgc cgc tgc aac	1357
Ser Pro Asn His Pro Leu Asp Ser Pro His Val Cys Arg Arg Cys Asn	
415 420 425 430	
tgc gag tcc gac ttc acg gat ggc acc tgc gag gac ctg acg ggt cga	1405
Cys Glu Ser Asp Phe Thr Asp Gly Thr Cys Glu Asp Leu Thr Gly Arg	
435 440 445	
tgc tac tgc cgg ccc aac ttc tct ggg gag cgg tgt gac gtg tgt gcc	1453
Cys Tyr Cys Arg Pro Asn Phe Ser Gly Glu Arg Cys Asp Val Cys Ala	
450 455 460	
gag ggc ttc acg ggc ttc cca agc tgc tac ccg acg ccc tcg tcc tcc	1501
Glu Gly Phe Thr Gly Phe Pro Ser Cys Tyr Pro Thr Pro Ser Ser Ser	
465 470 475	
aat gac acc agg gag cag gtg ctg cca gct ggc cag att gtg aat tgt	1549
Asn Asp Thr Arg Glu Gln Val Leu Pro Ala Gly Gln Ile Val Asn Cys	
480 485 490	
gac tgc agc gcg gca ggg acc cag ggc aac gcc tgc cgg aag gac cca	1597
Asp Cys Ser Ala Ala Gly Thr Gln Gly Asn Ala Cys Arg Lys Asp Pro	
495 500 505 510	
agg gtg gga cgc tgt ctg tgc aaa ccc aac ttc caa ggc acc cat tgt	1645
Arg Val Gly Arg Cys Leu Cys Lys Pro Asn Phe Gln Gly Thr His Cys	
515 520 525	
gag ctg tgc gcg cca ggg ttc tac ggc ccc ggc tgc cag ccc tgc cag	1693
Glu Leu Cys Ala Pro Gly Phe Tyr Gly Pro Gly Cys Gln Pro Cys Gln	
530 535 540	
tgt tcc agc cct gga gtg gcc gat gac cgc tgt gac cct gac aca ggc	1741
Cys Ser Ser Pro Gly Val Ala Asp Asp Arg Cys Asp Pro Asp Thr Gly	
545 550 555	
cag tgc agg tgc cga gtg ggc ttc gag ggg gcc aca tgt gat cgc tgt	1789
Gln Cys Arg Cys Arg Val Gly Phe Glu Gly Ala Thr Cys Asp Arg Cys	
560 565 570	

gcc ccc ggc tac ttt cac ttc cct ctc tgc cag ttg tgt ggc tgc agc	1837
Ala Pro Gly Tyr Phe His Phe Pro Leu Cys Gln Leu Cys Gly Cys Ser	
575	580 585 590
cct gca gga acc ttg ccc gag ggc tgc gat gag gcc ggc cgc tgc cta	1885
Pro Ala Gly Thr Leu Pro Glu Gly Cys Asp Glu Ala Gly Arg Cys Leu	
595	600 605
tgc cag cct gag ttt gct gga cct cat tgt gac cgg tgc cgc cct ggc	1933
Cys Gln Pro Glu Phe Ala Gly Pro His Cys Asp Arg Cys Arg Pro Gly	
610	615 620
tac cat ggt ttc ccc aac tgc caa gca tgc acc tgc gac cct cgg gga	1981
Tyr His Gly Phe Pro Asn Cys Gln Ala Cys Thr Cys Asp Pro Arg Gly	
625	630 635
gcc ctg gac cag ctc tgt ggg gcg gga ggt ttg tgc cgc tgc cgc ccc	2029
Ala Leu Asp Gln Leu Cys Gly Ala Gly Gly Leu Cys Arg Cys Arg Pro	
640	645 650
ggc tac aca ggc act gcc tgc cag gaa tgc agc ccc ggc ttt cac ggc	2077
Gly Tyr Thr Gly Thr Ala Cys Gln Glu Cys Ser Pro Gly Phe His Gly	
655	660 665 670
ttc ccc agc tgt gtc ccc tgc cac tgc tct gct gaa ggc tcc ctg cac	2125
Phe Pro Ser Cys Val Pro Cys His Cys Ser Ala Glu Gly Ser Leu His	
675	680 685
gca gcc tgt gac ccc egg agt ggg cag tgc agc tgc cgg ccc cgt gtg	2173
Ala Ala Cys Asp Pro Arg Ser Gly Gln Cys Ser Cys Arg Pro Arg Val	
690	695 700
acg ggg ctg cgg tgt gac acg tgt gtg ccc ggt gcc tac aac ttc ccc	2221
Thr Gly Leu Arg Cys Asp Thr Cys Val Pro Gly Ala Tyr Asn Phe Pro	
705	710 715
tac tgc gaa gct ggc tct tgc cac cct gcc ggt ctg gcc cca gtg gat	2269
Tyr Cys Glu Ala Gly Ser Cys His Pro Ala Gly Leu Ala Pro Val Asp	
720	725 730
cct gcc ctt cct gag gca cag gtt ccc tgt atg tgc cgg gct cac gtg	2317
Pro Ala Leu Pro Glu Ala Gln Val Pro Cys Met Cys Arg Ala His Val	
735	740 745 750
gag ggg ccg agc tgt gac cgc tgc aaa cct ggg ttc tgg gga ctg agc	2365
Glu Gly Pro Ser Cys Asp Arg Cys Lys Pro Gly Phe Trp Gly Leu Ser	
755	760 765
ccc agc aac ccc gag ggc tgt acc cgc tgc agc tgc gac ctc agg ggc	2413
Pro Ser Asn Pro Glu Gly Cys Thr Arg Cys Ser Cys Asp Leu Arg Gly	
770	775 780
aca ctg ggt gga gtt gct gag tgc cag ccg ggc acc ggc cag tgc ttc	2461
Thr Leu Gly Gly Val Ala Glu Cys Gln Pro Gly Thr Gly Gln Cys Phe	
785	790 795
tgc aag ccc cac gtg tgc ggc cag gcc tgc gcg tcc tgc aag gat ggc	2509
Cys Lys Pro His Val Cys Gly Gln Ala Cys Ala Ser Cys Lys Asp Gly	
800	805 810
ttc ttt gga ctg gat cag gct gac tat ttt ggc tgc cgc agc tgc cgg	2557

Phe 815	Phe	Gly	Leu	Asp	Gln 820	Ala	Asp	Tyr	Phe	Gly 825	Cys	Arg	Ser	Cys	Arg 830	
tgt	gac	att	ggc	ggg	gca	ctg	ggc	cag	agc	tgt	gaa	ccg	agg	acg	ggc	2605
Cys	Asp	Ile	Gly	Gly 835	Ala	Leu	Gly	Gln	Ser	Cys 840	Glu	Pro	Arg	Thr 845	Gly	
gtc	tgc	cgg	tgc	cgc	ccc	aac	acc	cag	ggc	ccc	acc	tgc	agc	gag	cct	2653
Val	Cys	Arg	Cys	Arg	Pro	Asn	Thr	Gln	Gly	Pro	Thr	Cys	Ser	Glu	Pro	
			850					855					860			
gcg	agg	gac	cac	tac	ctc	ccg	gac	ctg	cac	cac	ctg	cgc	ctg	gag	ctg	2701
Ala	Arg	Asp	His	Tyr	Leu	Pro	Asp	Leu	His	His	Leu	Arg	Leu	Glu	Leu	
		865					870					875				
gag	gag	gct	gcc	aca	cct	gag	ggg	cac	gcc	gtg	cgc	ttt	ggc	ttc	aac	2749
Glu	Glu	Ala	Ala	Thr	Pro	Glu	Gly	His	Ala	Val	Arg	Phe	Gly	Phe	Asn	
	880					885					890					
ccc	ctc	gag	ttc	gag	aac	ttc	agc	tgg	agg	ggc	tac	gcg	cag	atg	gca	2797
Pro	Leu	Glu	Phe	Glu	Asn	Phe	Ser	Trp	Arg	Gly	Tyr	Ala	Gln	Met	Ala	
895					900					905					910	
cct	gtc	cag	ccc	agg	atc	gtg	gcc	agg	ctg	aac	ctg	acc	tcc	ccc	gac	2845
Pro	Val	Gln	Pro	Arg	Ile	Val	Ala	Arg	Leu	Asn	Leu	Thr	Ser	Pro	Asp	
				915					920					925		
ctt	ttc	tgg	ctc	gtc	ttc	cga	tac	gtc	aac	cgg	ggg	gcc	atg	agt	gtg	2893
Leu	Phe	Trp	Leu	Val	Phe	Arg	Tyr	Val	Asn	Arg	Gly	Ala	Met	Ser	Val	
			930					935					940			
agc	ggg	cgg	gtc	tct	gtg	cga	gag	gag	ggc	agg	tcg	gcc	gcc	tgt	gcc	2941
Ser	Gly	Arg	Val	Ser	Val	Arg	Glu	Glu	Gly	Arg	Ser	Ala	Ala	Cys	Ala	
		945					950					955				
aac	tgc	aca	gca	cag	agt	cag	ccc	gtg	gcc	ttc	cca	ccc	agc	acg	gag	2989
Asn	Cys	Thr	Ala	Gln	Ser	Gln	Pro	Val	Ala	Phe	Pro	Pro	Ser	Thr	Glu	
	960					965					970					
cct	gcc	ttc	atc	acc	gtg	ccc	cag	agg	ggc	ttc	gga	gag	ccc	ttt	gtg	3037
Pro	Ala	Phe	Ile	Thr	Val	Pro	Gln	Arg	Gly	Phe	Gly	Glu	Pro	Phe	Val	
975					980				985					990		
ctg	aac	cct	ggc	acc	tgg	gcc	ctg	cgt	gtg	gag	gcc	gaa	ggg	gtg	ctc	3085
Leu	Asn	Pro	Gly	Thr	Trp	Ala	Leu	Arg	Val	Glu	Ala	Glu	Gly	Val	Leu	
				995				1000					1005			
ctg	gac	tac	gtg	ggt	ctg	ctg	cct	agc	gca	tac	tac	gag	gcg	gcg	ctc	3133
Leu	Asp	Tyr	Val	Val	Leu	Leu	Pro	Ser	Ala	Tyr	Tyr	Glu	Ala	Ala	Leu	
			1010					1015				1020				
ctg	cag	ctg	cgg	gtg	act	gag	gcc	tgc	aca	tac	cgt	ccc	tct	gcc	cag	3181
Leu	Gln	Leu	Arg	Val	Thr	Glu	Ala	Cys	Thr	Tyr	Arg	Pro	Ser	Ala	Gln	
	1025					1030					1035					
cag	tct	ggc	gac	aac	tgc	ctc	ctc	tac	aca	cac	ctc	ccc	ctg	gat	ggc	3229
Gln	Ser	Gly	Asp	Asn	Cys	Leu	Leu	Tyr	Thr	His	Leu	Pro	Leu	Asp	Gly	
	1040				1045					1050						
ttc	ccc	tcg	gcc	gcc	ggg	ctg	gag	gcc	ctg	tgt	cgc	cag	gac	aac	agc	3277
Phe	Pro	Ser	Ala	Ala	Gly	Leu	Glu	Ala	Leu	Cys	Arg	Gln	Asp	Asn	Ser	

1055	1060	1065	1070	
ctg ccc cgg ccc tgc ccc acg gag cag ctc agc ccg tcg cac ccg cca				3325
Leu Pro Arg Pro Cys Pro Thr Glu Gln Leu Ser Pro Ser His Pro Pro				
	1075	1080	1085	
ctg atc acc tgc acg ggc agt gat gtg gac gtc cag ctt caa gtg gca				3373
Leu Ile Thr Cys Thr Gly Ser Asp Val Asp Val Gln Leu Gln Val Ala				
	1090	1095	1100	
gtg cca cag cca ggc cgc tat gcc cta gtg gtg gag tac gcc aat gag				3421
Val Pro Gln Pro Gly Arg Tyr Ala Leu Val Val Glu Tyr Ala Asn Glu				
	1105	1110	1115	
gat gcc cgc cag gag gtg ggc gtg gct gtg cac acc cca cag cgg gcc				3469
Asp Ala Arg Gln Glu Val Gly Val Ala Val His Thr Pro Gln Arg Ala				
	1120	1125	1130	
ccc cag cag ggg ctg ctc tcc ctg cac ccc tgc ctg tac agc acc ctg				3517
Pro Gln Gln Gly Leu Leu Ser Leu His Pro Cys Leu Tyr Ser Thr Leu				
	1135	1140	1145	1150
tgc cgg ggc act gcc cgg gat acc cag gac cac ctg gct gtc ttc cac				3565
Cys Arg Gly Thr Ala Arg Asp Thr Gln Asp His Leu Ala Val Phe His				
	1155	1160	1165	
ctg gac tcg gag gcc agc gtg agg ctc aca gcc gag cag gca cgc ttc				3613
Leu Asp Ser Glu Ala Ser Val Arg Leu Thr Ala Glu Gln Ala Arg Phe				
	1170	1175	1180	
ttc ctg cac ggg gtc act ctg gtg ccc att gag gag ttc agc ccg gag				3661
Phe Leu His Gly Val Thr Leu Val Pro Ile Glu Glu Phe Ser Pro Glu				
	1185	1190	1195	
ttc gtg gag ccc cgg gtc agc tgc atc agc agc cac ggc gcc ttt ggc				3709
Phe Val Glu Pro Arg Val Ser Cys Ile Ser Ser His Gly Ala Phe Gly				
	1200	1205	1210	
ccc aac agt gcc gcc tgt ctg ccc tcg cgc ttc cca aag ccg ccc cag				3757
Pro Asn Ser Ala Ala Cys Leu Pro Ser Arg Phe Pro Lys Pro Pro Gln				
	1215	1220	1225	1230
ccc atc atc ctc agg gac tgc cag gtg atc ccg ctg ccg ccc ggc ctc				3805
Pro Ile Ile Leu Arg Asp Cys Gln Val Ile Pro Leu Pro Pro Gly Leu				
	1235	1240	1245	
ccg ctg acc cac gcg cag gat ctc act cca gcc acg tcc cca gct gga				3853
Pro Leu Thr His Ala Gln Asp Leu Thr Pro Ala Thr Ser Pro Ala Gly				
	1250	1255	1260	
ccc cga cct cgg ccc ccc acc gct gtg gac cct gat gca gag ccc acc				3901
Pro Arg Pro Arg Pro Pro Thr Ala Val Asp Pro Asp Ala Glu Pro Thr				
	1265	1270	1275	
ctg ctg cgt gag ccc cag gcc acc gtg gtc ttc acc acc cat gtg ccc				3949
Leu Leu Arg Glu Pro Gln Ala Thr Val Val Phe Thr Thr His Val Pro				
	1280	1285	1290	
acg ctg ggc cgc tat gcc ttc ctg ctg cac ggc tac cag cca gcc cac				3997
Thr Leu Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro Ala His				
	1295	1300	1305	1310

ccc acc ttc ccc gtg gaa gtc ctc atc aac gcc ggc cgc gtg tgg cag 4045
Pro Thr Phe Pro Val Glu Val Leu Ile Asn Ala Gly Arg Val Trp Gln
1315 1320 1325

ggc cac gcc aac gcc agc ttc tgt cca cat ggc tac ggc tgc cgc acc 4093
Gly His Ala Asn Ala Ser Phe Cys Pro His Gly Tyr Gly Cys Arg Thr
1330 1335 1340

ctg gtg gtg tgt gag ggc cag gcc ctg ctg gac gtg acc cac agc gag 4141
Leu Val Val Cys Glu Gly Gln Ala Leu Leu Asp Val Thr His Ser Glu
1345 1350 1355

ctc act gtg acc gtg cgt gtg ccc gag ggc cgg tgg ctc tgg ctg gat 4189
Leu Thr Val Thr Val Arg Val Pro Glu Gly Arg Trp Leu Trp Leu Asp
1360 1365 1370

tat gta ctc gtg gtc cct gag aac gtc tac agc ttt ggc tac ctc cgg 4237
Tyr Val Leu Val Val Pro Glu Asn Val Tyr Ser Phe Gly Tyr Leu Arg
1375 1380 1385 1390

gag gag ccc ctg gat aaa tcc tat gac ttc atc agc cac tgc gca gcc 4285
Glu Glu Pro Leu Asp Lys Ser Tyr Asp Phe Ile Ser His Cys Ala Ala
1395 1400 1405

cag ggc tac cac atc agc ccc agc agc tca tcc ctg ttc tgc cga aac 4333
Gln Gly Tyr His Ile Ser Pro Ser Ser Ser Ser Leu Phe Cys Arg Asn
1410 1415 1420

gct gct gct tcc ctc tcc ctc ttc tat aac aac gga gcc cgt cca tgt 4381
Ala Ala Ala Ser Leu Ser Leu Phe Tyr Asn Asn Gly Ala Arg Pro Cys
1425 1430 1435

ggc tgc cac gaa gta ggt gct aca ggc ccc acg tgt gag ccc ttc ggg 4429
Gly Cys His Glu Val Gly Ala Thr Gly Pro Thr Cys Glu Pro Phe Gly
1440 1445 1450

ggc cag tgt ccc tgc cat gcc cat gtc att ggc cgt gac tgc tcc cgc 4477
Gly Gln Cys Pro Cys His Ala His Val Ile Gly Arg Asp Cys Ser Arg
1455 1460 1465 1470

tgt gcc acc gga tac tgg ggc ttc ccc aac tgc agg ccc tgt gac tgc 4525
Cys Ala Thr Gly Tyr Trp Gly Phe Pro Asn Cys Arg Pro Cys Asp Cys
1475 1480 1485

ggt gcc cgc ctc tgt gac gag ctc acg ggc cag tgc atc tgc ccg cca 4573
Gly Ala Arg Leu Cys Asp Glu Leu Thr Gly Gln Cys Ile Cys Pro Pro
1490 1495 1500

cgc acc atc ccg ccc gac tgc ctg ctg tgc cag ccc cag acc ttt ggc 4621
Arg Thr Ile Pro Pro Asp Cys Leu Leu Cys Gln Pro Gln Thr Phe Gly
1505 1510 1515

tgc cac ccc ctg gtc ggc tgt gag gag tgt aac tgc tca ggg ccc ggc 4669
Cys His Pro Leu Val Gly Cys Glu Glu Cys Asn Cys Ser Gly Pro Gly
1520 1525 1530

atc cag gag ctc aca gac cct acc tgt gac aca gac agc ggc cag tgc 4717
Ile Gln Glu Leu Thr Asp Pro Thr Cys Asp Thr Asp Ser Gly Gln Cys
1535 1540 1545 1550

aag tgc aga ccc aac gtg act ggg cgc cgc tgt gat acc tgc tct ccg 4765
Lys Cys Arg Pro Asn Val Thr Gly Arg Arg Cys Asp Thr Cys Ser Pro
1555 1560 1565

ggc ttc cat ggc tac ccc cgc tgc cgc ccc tgt gac tgt cac gag gcg 4813
Gly Phe His Gly Tyr Pro Arg Cys Arg Pro Cys Asp Cys His Glu Ala
1570 1575 1580

ggc act gcg cct ggc gtg tgt gac ccc ctc aca ggg cag tgc tac tgt 4861
Gly Thr Ala Pro Gly Val Cys Asp Pro Leu Thr Gly Gln Cys Tyr Cys
1585 1590 1595

aag gag aac gtg cag ggc ccc aaa tgt gac cag tgc agc ctt ggg acc 4909
Lys Glu Asn Val Gln Gly Pro Lys Cys Asp Gln Cys Ser Leu Gly Thr
1600 1605 1610

ttc tca ctg gat gct gcc aac ccc aaa ggt tgc acc cgc tgc ttc tgc 4957
Phe Ser Leu Asp Ala Ala Asn Pro Lys Gly Cys Thr Arg Cys Phe Cys
1615 1620 1625 1630

ttt ggg gcc acg gag cgc tgc cgg agc tgc tcc tac acc cgc cag gag 5005
Phe Gly Ala Thr Glu Arg Cys Arg Ser Ser Ser Tyr Thr Arg Gln Glu
1635 1640 1645

ttc gtg gat atg gag gga tgg gtg ctg ctg agc act gac cgg cag gtg 5053
Phe Val Asp Met Glu Gly Trp Val Leu Leu Ser Thr Asp Arg Gln Val
1650 1655 1660

gtg ccc cac gag cgg cag cca ggg acg gag atg ctc cgt gca gac ctg 5101
Val Pro His Glu Arg Gln Pro Gly Thr Glu Met Leu Arg Ala Asp Leu
1665 1670 1675

cgg cac gtg cct gag gct gtg ccc gag gct ttc ccc gag ctg tac tgg 5149
Arg His Val Pro Glu Ala Val Pro Glu Ala Phe Pro Glu Leu Tyr Trp
1680 1685 1690

cag gcc cca ccc tcc tac ctg ggg gac cgg gtg tca tcc tac ggt ggg 5197
Gln Ala Pro Pro Ser Tyr Leu Gly Asp Arg Val Ser Ser Tyr Gly Gly
1695 1700 1705 1710

acc ctc cgt tat gaa ctg cac tca gag acc cag cgg gga gat gtc ttt 5245
Thr Leu Arg Tyr Glu Leu His Ser Glu Thr Gln Arg Gly Asp Val Phe
1715 1720 1725

gtc ccc atg gag agc agg ccg gat gtg gtg ctg cag ggc aac cag atg 5293
Val Pro Met Glu Ser Arg Pro Asp Val Val Leu Gln Gly Asn Gln Met
1730 1735 1740

agc atc aca ttc ctg gag ccg gca tac ccc acg cct ggc cac gtt cac 5341
Ser Ile Thr Phe Leu Glu Pro Ala Tyr Pro Thr Pro Gly His Val His
1745 1750 1755

cgt ggg cag ctg cag ctg gtg gag ggg aac ttc cgg cat acg gag act 5389
Arg Gly Gln Leu Gln Leu Val Glu Gly Asn Phe Arg His Thr Glu Thr
1760 1765 1770

cgc aac act gtg tcc cgc gag gag ctc atg atg gtg ctg gcc agc ctg 5437
Arg Asn Thr Val Ser Arg Glu Glu Leu Met Met Val Leu Ala Ser Leu
1775 1780 1785 1790

gag cag ctg cag atc cgt gcc ctc ttc tca cag atc tcc tgc gct gtc 5485

Glu	Gln	Leu	Gln	Ile	Arg	Ala	Leu	Phe	Ser	Gln	Ile	Ser	Ser	Ala	Val		
				1795					1800					1805			
tcc	ctg	cgc	agg	gtg	gca	ctg	gag	gtg	gcc	agc	cca	gca	ggc	cag	ggg	5533	
Ser	Leu	Arg	Arg	Val	Ala	Leu	Glu	Val	Ala	Ser	Pro	Ala	Gly	Gln	Gly		
			1810					1815					1820				
gcc	ctg	gcc	agc	aat	gtg	gag	ctg	tgc	ctg	tgc	ccc	gcc	agc	tac	cgg	5581	
Ala	Leu	Ala	Ser	Asn	Val	Glu	Leu	Cys	Leu	Cys	Pro	Ala	Ser	Tyr	Arg		
			1825					1830						1835			
ggg	gac	tca	tgc	cag	gaa	tgt	gcc	ccc	ggc	ttc	tat	cgg	gac	gtc	aaa	5629	
Gly	Asp	Ser	Cys	Gln	Glu	Cys	Ala	Pro	Gly	Phe	Tyr	Arg	Asp	Val	Lys		
			1840				1845					1850					
ggt	ctc	ttc	ctg	ggc	cga	tgt	gtc	cct	tgt	cag	tgc	cat	gga	cac	tca	5677	
Gly	Leu	Phe	Leu	Gly	Arg	Cys	Val	Pro	Cys	Gln	Cys	His	Gly	His	Ser		
			1855			1860					1865					1870	
gac	cgc	tgc	ctc	cct	ggc	tct	ggc	gtc	tgt	gtg	gac	tgc	cag	cac	aac	5725	
Asp	Arg	Cys	Leu	Pro	Gly	Ser	Gly	Val	Cys	Val	Asp	Cys	Gln	His	Asn		
				1875					1880						1885		
acc	gaa	ggg	gcc	cac	tgt	gag	cgc	tgc	cag	gct	ggc	ttc	atg	agc	agc	5773	
Thr	Glu	Gly	Ala	His	Cys	Glu	Arg	Cys	Gln	Ala	Gly	Phe	Met	Ser	Ser		
				1890					1895					1900			
agg	gac	gac	ccc	agc	gcc	ccc	tgt	gtc	agc	tgc	ccc	tgc	ccc	ctc	tca	5821	
Arg	Asp	Asp	Pro	Ser	Ala	Pro	Cys	Val	Ser	Cys	Pro	Cys	Pro	Leu	Ser		
			1905					1910					1915				
gtg	cct	tcc	aac	aac	ttc	gcc	gag	ggc	tgt	gtc	ctg	cga	ggc	ggc	cgc	5869	
Val	Pro	Ser	Asn	Asn	Phe	Ala	Glu	Gly	Cys	Val	Leu	Arg	Gly	Gly	Arg		
			1920					1925				1930					
acc	cag	tgc	ctc	tgc	aaa	cct	ggt	tat	gca	ggt	gcc	tcc	tgc	gag	cgg	5917	
Thr	Gln	Cys	Leu	Cys	Lys	Pro	Gly	Tyr	Ala	Gly	Ala	Ser	Cys	Glu	Arg		
			1935			1940					1945				1950		
tgt	gcg	ccc	gga	ttc	ttt	ggg	aac	cca	ctg	gtg	ctg	ggc	agc	tcc	tgc	5965	
Cys	Ala	Pro	Gly	Phe	Phe	Gly	Asn	Pro	Leu	Val	Leu	Gly	Ser	Ser	Cys		
				1955					1960						1965		
cag	cca	tgc	gac	tgc	agc	ggc	aac	ggt	gac	ccc	aac	ttg	ctc	ttc	agc	6013	
Gln	Pro	Cys	Asp	Cys	Ser	Gly	Asn	Gly	Asp	Pro	Asn	Leu	Leu	Phe	Ser		
				1970					1975						1980		
gac	tgc	gac	ccc	ctg	acg	ggc	gcc	tgc	cgt	ggc	tgc	ctg	cgc	cac	acc	6061	
Asp	Cys	Asp	Pro	Leu	Thr	Gly	Ala	Cys	Arg	Gly	Cys	Leu	Arg	His	Thr		
			1985					1990						1995			
act	ggg	ccc	cgc	tgc	gag	atc	tgt	gcc	ccc	ggc	ttc	tac	ggc	aac	gcc	6109	
Thr	Gly	Pro	Arg	Cys	Glu	Ile	Cys	Ala	Pro	Gly	Phe	Tyr	Gly	Asn	Ala		
			2000					2005					2010				
ctg	ctg	ccc	ggc	aac	tgc	acc	cgg	tgc	gac	tgt	acc	cca	tgt	ggg	aca	6157	
Leu	Leu	Pro	Gly	Asn	Cys	Thr	Arg	Cys	Asp	Cys	Thr	Pro	Cys	Gly	Thr		
						2020					2025				2030		
gag	gcc	tgc	gac	ccc	cac	agc	ggg	cac	tgc	ctg	tgc	aag	gcg	ggc	gtg	6205	
Glu	Ala	Cys	Asp	Pro	His	Ser	Gly	His	Cys	Leu	Cys	Lys	Ala	Gly	Val		

2035	2040	2045	
act ggg cgg cgc tgt gac cgc tgc cag gag gga cat ttt ggt ttc aat			6253
Thr Gly Arg Arg Cys Asp Arg Cys Gln Glu Gly His Phe Gly Phe Asn			
2050	2055	2060	
ggc tgc ggg ggc tgc cgc ccg tgt gct tgt gga ccg gcc gcc gag ggc			6301
Gly Cys Gly Gly Cys Arg Pro Cys Ala Cys Gly Pro Ala Ala Glu Gly			
2065	2070	2075	
tcc gag tgc cac ccc cag agc gga cag tgc cac tgc cga cca ggg acc			6349
Ser Glu Cys His Pro Gln Ser Gly Gln Cys His Cys Arg Pro Gly Thr			
2080	2085	2090	
atg gga ccc cag tgc cgc gag tgt gcc cct ggc tac tgg ggg ctc cct			6397
Met Gly Pro Gln Cys Arg Glu Cys Ala Pro Gly Tyr Trp Gly Leu Pro			
2095	2100	2105	2110
gag cag ggc tgc agg cgc tgc cag tgc cct ggg ggc cgc tgt gac cct			6445
Glu Gln Gly Cys Arg Arg Cys Gln Cys Pro Gly Gly Arg Cys Asp Pro			
2115	2120	2125	
cac acg ggc cgc tgc aac tgc ccc ccg ggg ctc agc ggg gag cgc tgc			6493
His Thr Gly Arg Cys Asn Cys Pro Pro Gly Leu Ser Gly Glu Arg Cys			
2130	2135	2140	
gac acc tgc agc cag cag cat cag gtg cct gtt cca ggc ggg cct gtg			6541
Asp Thr Cys Ser Gln Gln His Gln Val Pro Val Pro Gly Gly Pro Val			
2145	2150	2155	
ggc cac agc atc cac tgt gaa gtg tgt gac cac tgt gtg gtc ctg ctc			6589
Gly His Ser Ile His Cys Glu Val Cys Asp His Cys Val Val Leu Leu			
2160	2165	2170	
ctg gat gac ctg gaa ccg gcc ggc gcc ctc ctc ccc gcc att cac gag			6637
Leu Asp Asp Leu Glu Arg Ala Gly Ala Leu Leu Pro Ala Ile His Glu			
2175	2180	2185	2190
caa ctg cgt ggc atc aat gcc agc tcc atg gcc tgg gcc cgt ctg cac			6685
Gln Leu Arg Gly Ile Asn Ala Ser Ser Met Ala Trp Ala Arg Leu His			
2195	2200	2205	
agg ctg aac gcc tcc atc gct gac ctg cag agc cag ctc cgg agc ccc			6733
Arg Leu Asn Ala Ser Ile Ala Asp Leu Gln Ser Gln Leu Arg Ser Pro			
2210	2215	2220	
ctg ggc ccc cgc cat gag acg gca cag cag ctg gag gtg ctg gag cag			6781
Leu Gly Pro Arg His Glu Thr Ala Gln Gln Leu Glu Val Leu Glu Gln			
2225	2230	2235	
cag agc aca agc ctc ggg cag gac gca ccg ccg cta ggc ggc cag gcc			6829
Gln Ser Thr Ser Leu Gly Gln Asp Ala Arg Arg Leu Gly Gly Gln Ala			
2240	2245	2250	
gtg ggg acc cga gac cag gcg agc caa ttg ctg gcc gcc acc gag gcc			6877
Val Gly Thr Arg Asp Gln Ala Ser Gln Leu Leu Ala Gly Thr Glu Ala			
2255	2260	2265	2270
aca ctg ggc cat gcg aag acg ctg ttg gcg gcc atc ccg gct gtg gac			6925
Thr Leu Gly His Ala Lys Thr Leu Leu Ala Ala Ile Arg Ala Val Asp			
2275	2280	2285	

cgc acc ctg agc gag ctc atg tcc cag acg ggc cac ctg ggg ctg gcc Arg Thr Leu Ser Glu Leu Met Ser Gln Thr Gly His Leu Gly Leu Ala 2290 2295 2300	6973
aat gcc tcg gct cca tca ggt gag cag ctg ctc cgg aca ctg gcc gag Asn Ala Ser Ala Pro Ser Gly Glu Gln Leu Leu Arg Thr Leu Ala Glu 2305 2310 2315	7021
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cgg gtg cag gag cag ctg agc agc ctc tgg gag gag aac cag gca ctg Arg Val Gln Glu Gln Leu Ser Ser Leu Trp Glu Glu Asn Gln Ala Leu 2355 2360 2365	7165
gcc aca caa acc cgc gac cgg ctg gcc cag cac gag gcc ggc ctc atg Ala Thr Gln Thr Arg Asp Arg Leu Ala Gln His Glu Ala Gly Leu Met 2370 2375 2380	7213
gac ctg cga gag gct ttg aac cgg gca gtg gac gcc aca cgg gag gcc Asp Leu Arg Glu Ala Leu Asn Arg Ala Val Asp Ala Thr Arg Glu Ala 2385 2390 2395	7261
cag gag ctc aac agc cgc aac cag gag cgc ctg gag gaa gcc ctg caa Gln Glu Leu Asn Ser Arg Asn Gln Glu Arg Leu Glu Glu Ala Leu Gln 2400 2405 2410	7309
agg aag cag gag ctg tcc cgg gac aat gcc acc ctg cag gcc act ctg Arg Lys Gln Glu Leu Ser Arg Asp Asn Ala Thr Leu Gln Ala Thr Leu 2415 2420 2425 2430	7357
cat gcg gct agg gac acc ctg gcc agc gtc ttc aga ttg ctg cac agc His Ala Ala Arg Asp Thr Leu Ala Ser Val Phe Arg Leu Leu His Ser 2435 2440 2445	7405
ctg gac cag gct aag gag gag ctg gag cgc ctc gcc gcc agc ctg gac Leu Asp Gln Ala Lys Glu Glu Leu Glu Arg Leu Ala Ala Ser Leu Asp 2450 2455 2460	7453
ggg gct cgg acc cca ctg ctg cag agg atg cag acc ttc tcc ccg gcg Gly Ala Arg Thr Pro Leu Leu Gln Arg Met Gln Thr Phe Ser Pro Ala 2465 2470 2475	7501
ggc agc aag ctg cgt cta gtg gag gcc gcc gag gcc cac gca cag cag Gly Ser Lys Leu Arg Leu Val Glu Ala Ala Glu Ala His Ala Gln Gln 2480 2485 2490	7549
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2530 2535 2540	
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Leu Gln Gln Ala Asp His Thr Trp Ala Thr Val Val Arg Gln Gly Leu	
2545 2550 2555	
gtg gac cga gcc cag cag ctc ctg gcc aac agc act gca cta gaa gag	7789
Val Asp Arg Ala Gln Gln Leu Leu Ala Asn Ser Thr Ala Leu Glu Glu	
2560 2565 2570	
gcc atg ctc cag gaa cag cag agg ctg ggc ctt gtg tgg gct gcc ctc	7837
Ala Met Leu Gln Glu Gln Gln Arg Leu Gly Leu Val Trp Ala Ala Leu	
2575 2580 2585 2590	
cag ggt gcc agg acc cag ctc cga gat gtc cgg gcc aag aag gac cag	7885
Gln Gly Ala Arg Thr Gln Leu Arg Asp Val Arg Ala Lys Lys Asp Gln	
2595 2600 2605	
ctg gag gcg cac atc cag gcg gcg cag gcc atg ctt gcc atg gac aca	7933
Leu Glu Ala His Ile Gln Ala Ala Gln Ala Met Leu Ala Met Asp Thr	
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gac gag aca agc aag aag atc gca cat gcc aag gct gtg gct gct gaa	7981
Asp Glu Thr Ser Lys Lys Ile Ala His Ala Lys Ala Val Ala Ala Glu	
2625 2630 2635	
gcc cag gac acc gcc acc cgt gtg cag tcc cag ctg cag gcc atg cag	8029
Ala Gln Asp Thr Ala Thr Arg Val Gln Ser Gln Leu Gln Ala Met Gln	
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Glu Asn Val Glu Arg Trp Gln Gly Gln Tyr Glu Gly Leu Arg Gly Gln	
2655 2660 2665 2670	
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Asp Leu Gly Gln Ala Val Leu Asp Ala Gly His Ser Val Ser Thr Leu	
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Arg Gly Val His Asn Ala Ser Leu Ala Leu Ser Ala Ser Ile Gly Arg	
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Val Arg Glu Leu Ile Ala Gln Ala Arg Gly Ala Ala Ser Lys Val Lys	
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Val Pro Met Lys Phe Asn Gly Arg Ser Gly Val Gln Leu Arg Thr Pro	
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Gln Gly Pro Glu Pro Glu Pro Gly Gln Gly Thr Glu Asp Arg Phe Val	
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Leu Arg Asp Lys Lys Val His Trp Val Tyr Gln Leu Gly Glu Ala Gly	
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Pro Ala Val Leu Ser Ile Asp Glu Asp Ile Gly Glu Gln Phe Ala Ala	
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Val Ser Leu Asp Arg Thr Leu Gln Phe Gly His Met Ser Val Thr Val	
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Ser Leu Tyr Asn Phe Glu Arg Thr Phe Gln Leu Asp Thr Ala Val Asp	
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Gln Ile Ser Thr Thr Lys Arg Phe Glu Gln Glu Leu Arg Leu Val Ser	
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Tyr Ser Gly Val Leu Phe Phe Leu Lys Gln Gln Ser Gln Phe Leu Cys	
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Gly Leu Lys Lys Ala Val Pro Leu Gln Pro Pro Pro Pro Leu Thr Ser	

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Ala Ser Lys Ala Ile Gln Val Phe Leu Leu Gly Gly Ser Arg Lys Arg			
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Val Leu Val Arg Val Glu Arg Ala Thr Val Tyr Ser Val Glu Gln Asp			
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Asn Asp Leu Glu Leu Ala Asp Ala Tyr Tyr Leu Gly Gly Val Pro Pro			
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Asp Gln Leu Pro Pro Ser Leu Arg Trp Leu Phe Pro Thr Gly Gly Ser			
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Phe Gly Phe His Ser Ala Gln Asp Ser Ala Leu Leu Tyr Tyr Arg Ala			
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Ser Pro Asp Gly Leu Cys Gln Val Ser Leu Gln Gln Gly Arg Val Ser			
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Gly Ala Pro His Tyr Val Ala Phe Tyr Ser Asn Ala Thr Gly Val Trp			
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 Tyr Phe Asn Leu Ala Glu Gly Ala Arg Ile Ala Ala Ser Ala Thr Cys
 50 55 60
 Gly Glu Glu Ala Pro Ala Arg Gly Ser Pro Arg Pro Thr Glu Asp Leu
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 Tyr Cys Lys Leu Val Gly Gly Pro Val Ala Gly Gly Asp Pro Asn Gln
 85 90 95
 Thr Ile Arg Gly Gln Tyr Cys Asp Ile Cys Thr Ala Ala Asn Ser Asn
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 Lys Ala His Pro Ala Ser Asn Ala Ile Asp Gly Thr Glu Arg Trp Trp
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 Phe Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg Ser Met
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 Asp Phe Gly Arg Thr Tyr Gln Pro Trp Gln Phe Phe Ala Ser Ser Lys
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 Arg Asp Asp Ala Ala Ile Cys Thr Thr Glu Tyr Ser Arg Ile Val Pro
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 Ala Met Asn Phe Ser Tyr Ser Pro Leu Leu Arg Glu Phe Thr Lys Ala
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 Thr Asn Val Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu Gly His
 260 265 270
 Leu Met Gly Lys Ala Leu Arg Asp Pro Thr Val Thr Arg Arg Tyr Tyr
 275 280 285
 Tyr Ser Ile Lys Asp Ile Ser Ile Gly Gly Arg Cys Val Cys His Gly
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His Ala Asp Ala Cys Asp Ala Lys Asp Pro Thr Asp Pro Phe Arg Leu
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 Gln Cys Thr Cys Gln His Asn Thr Cys Gly Gly Thr Cys Asp Arg Cys
 325 330 335
 Cys Pro Gly Phe Asn Gln Gln Pro Trp Lys Pro Ala Thr Ala Asn Ser
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 Ala Asn Glu Cys Gln Ser Cys Asn Cys Tyr Gly His Ala Thr Asp Cys
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 Tyr Tyr Asp Pro Glu Val Asp Arg Arg Arg Ala Ser Gln Ser Leu Asp
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 Gly Thr Tyr Gln Gly Gly Gly Val Cys Ile Asp Cys Gln His His Thr
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 Ala Gly Val Asn Cys Glu Arg Cys Leu Pro Gly Phe Tyr Arg Ser Pro
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 Asn His Pro Leu Asp Ser Pro His Val Cys Arg Arg Cys Asn Cys Glu
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 Ser Asp Phe Thr Asp Gly Thr Cys Glu Asp Leu Thr Gly Arg Cys Tyr
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 Cys Arg Pro Asn Phe Ser Gly Glu Arg Cys Asp Val Cys Ala Glu Gly
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 Phe Thr Gly Phe Pro Ser Cys Tyr Pro Thr Pro Ser Ser Ser Asn Asp
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 Ser Ala Ala Gly Thr Gln Gly Asn Ala Cys Arg Lys Asp Pro Arg Val
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 Gly Arg Cys Leu Cys Lys Pro Asn Phe Gln Gly Thr His Cys Glu Leu
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 Arg Cys Arg Val Gly Phe Glu Gly Ala Thr Cys Asp Arg Cys Ala Pro
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 Gly Tyr Phe His Phe Pro Leu Cys Gln Leu Cys Gly Cys Ser Pro Ala
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 Gly Thr Leu Pro Glu Gly Cys Asp Glu Ala Gly Arg Cys Leu Cys Gln
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 Pro Glu Phe Ala Gly Pro His Cys Asp Arg Cys Arg Pro Gly Tyr His
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 Gly Phe Pro Asn Cys Gln Ala Cys Thr Cys Asp Pro Arg Gly Ala Leu

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Pro	His	Val	Cys	Gly	Gln	Ala	Cys	Ala	Ser	Cys	Lys	Asp	Gly	Phe	Phe	
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Gly	Leu	Asp	Gln	Ala	Asp	Tyr	Phe	Gly	Cys	Arg	Ser	Cys	Arg	Cys	Asp	
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Asp	His	Tyr	Leu	Pro	Asp	Leu	His	His	Leu	Arg	Leu	Glu	Leu	Glu	Glu	
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Ala	Ala	Thr	Pro	Glu	Gly	His	Ala	Val	Arg	Phe	Gly	Phe	Asn	Pro	Leu	
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Glu	Phe	Glu	Asn	Phe	Ser	Trp	Arg	Gly	Tyr	Ala	Gln	Met	Ala	Pro	Val	
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Gln	Pro	Arg	Ile	Val	Ala	Arg	Leu	Asn	Leu	Thr	Ser	Pro	Asp	Leu	Phe	
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 Phe Ile Thr Val Pro Gln Arg Gly Phe Gly Glu Pro Phe Val Leu Asn
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 Pro Gly Thr Trp Ala Leu Arg Val Glu Ala Glu Gly Val Leu Leu Asp
 995 1000 1005
 Tyr Val Val Leu Leu Pro Ser Ala Tyr Tyr Glu Ala Ala Leu Leu Gln
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 1125 1130 1135
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 Gly Thr Ala Arg Asp Thr Gln Asp His Leu Ala Val Phe His Leu Asp
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 His Gly Val Thr Leu Val Pro Ile Glu Glu Phe Ser Pro Glu Phe Val
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 Glu Pro Arg Val Ser Cys Ile Ser Ser His Gly Ala Phe Gly Pro Asn
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 Ile Leu Arg Asp Cys Gln Val Ile Pro Leu Pro Pro Gly Leu Pro Leu
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 Thr His Ala Gln Asp Leu Thr Pro Ala Thr Ser Pro Ala Gly Pro Arg
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 Pro Arg Pro Pro Thr Ala Val Asp Pro Asp Ala Glu Pro Thr Leu Leu
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Arg Glu Pro Gln Ala Thr Val Val Phe Thr Thr His Val Pro Thr Leu
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Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro Ala His Pro Thr
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Phe Pro Val Glu Val Leu Ile Asn Ala Gly Arg Val Trp Gln Gly His
 1315 1320 1325

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

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Asp Met Glu Gly Trp Val Leu Leu Ser Thr Asp Arg Gln Val Val Pro		
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His Glu Arg Gln Pro Gly Thr Glu Met Leu Arg Ala Asp Leu Arg His		
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Val Pro Glu Ala Val Pro Glu Ala Phe Pro Glu Leu Tyr Trp Gln Ala		
1685	1690	1695
Pro Pro Ser Tyr Leu Gly Asp Arg Val Ser Ser Tyr Gly Gly Thr Leu		
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Arg Tyr Glu Leu His Ser Glu Thr Gln Arg Gly Asp Val Phe Val Pro		
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Met Glu Ser Arg Pro Asp Val Val Leu Gln Gly Asn Gln Met Ser Ile		
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Thr Phe Leu Glu Pro Ala Tyr Pro Thr Pro Gly His Val His Arg Gly		
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Gln Leu Gln Leu Val Glu Gly Asn Phe Arg His Thr Glu Thr Arg Asn		
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Thr Val Ser Arg Glu Glu Leu Met Met Val Leu Ala Ser Leu Glu Gln		
1780	1785	1790
Leu Gln Ile Arg Ala Leu Phe Ser Gln Ile Ser Ser Ala Val Ser Leu		
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Ser Cys Gln Glu Cys Ala Pro Gly Phe Tyr Arg Asp Val Lys Gly Leu		
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Phe Leu Gly Arg Cys Val Pro Cys Gln Cys His Gly His Ser Asp Arg		
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Cys Leu Pro Gly Ser Gly Val Cys Val Asp Cys Gln His Asn Thr Glu		
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1890	1895	1900
Asp Pro Ser Ala Pro Cys Val Ser Cys Pro Cys Pro Leu Ser Val Pro		
1905	1910	1920
Ser Asn Asn Phe Ala Glu Gly Cys Val Leu Arg Gly Gly Arg Thr Gln		
1925	1930	1935

Cys Leu Cys Lys Pro Gly Tyr Ala Gly Ala Ser Cys Glu Arg Cys Ala
 1940 1945 1950

Pro Gly Phe Phe Gly Asn Pro Leu Val Leu Gly Ser Ser Cys Gln Pro
 1955 1960 1965

Cys Asp Cys Ser Gly Asn Gly Asp Pro Asn Leu Leu Phe Ser Asp Cys
 1970 1975 1980

Asp Pro Leu Thr Gly Ala Cys Arg Gly Cys Leu Arg His Thr Thr Gly
 1985 1990 1995 2000

Pro Arg Cys Glu Ile Cys Ala Pro Gly Phe Tyr Gly Asn Ala Leu Leu
 2005 2010 2015

Pro Gly Asn Cys Thr Arg Cys Asp Cys Thr Pro Cys Gly Thr Glu Ala
 2020 2025 2030

Cys Asp Pro His Ser Gly His Cys Leu Cys Lys Ala Gly Val Thr Gly
 2035 2040 2045

Arg Arg Cys Asp Arg Cys Gln Glu Gly His Phe Gly Phe Asn Gly Cys
 2050 2055 2060

Gly Gly Cys Arg Pro Cys Ala Cys Gly Pro Ala Ala Glu Gly Ser Glu
 2065 2070 2075 2080

Cys His Pro Gln Ser Gly Gln Cys His Cys Arg Pro Gly Thr Met Gly
 2085 2090 2095

Pro Gln Cys Arg Glu Cys Ala Pro Gly Tyr Trp Gly Leu Pro Glu Gln
 2100 2105 2110

Gly Cys Arg Arg Cys Gln Cys Pro Gly Gly Arg Cys Asp Pro His Thr
 2115 2120 2125

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

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Thr Ser Lys Lys Ile Ala His Ala Lys Ala Val Ala Ala Glu Ala Gln 2625	2630	2635 2640
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Gly Gln Ala Val Leu Asp Ala Gly His Ser Val Ser Thr Leu Glu Lys 2675	2680	2685
Thr Leu Pro Gln Leu Leu Ala Lys Leu Ser Ile Leu Glu Asn Arg Gly 2690	2695	2700
Val His Asn Ala Ser Leu Ala Leu Ser Ala Ser Ile Gly Arg Val Arg 2705	2710	2715 2720
Glu Leu Ile Ala Gln Ala Arg Gly Ala Ala Ser Lys Val Lys Val Pro 2725	2730	2735
Met Lys Phe Asn Gly Arg Ser Gly Val Gln Leu Arg Thr Pro Arg Asp 2740	2745	2750
Leu Ala Asp Leu Ala Ala Tyr Thr Ala Leu Lys Phe Tyr Leu Gln Gly 2755	2760	2765
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Met Gly Ser Arg Gln Ala Thr Gly Asp Tyr Met Gly Val Ser Leu Arg 2785	2790	2795 2800
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Val Leu Ser Ile Asp Glu Asp Ile Gly Glu Gln Phe Ala Ala Val Ser 2820	2825	2830
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Gln Met Ile Gln Glu Thr Lys Gly Asp Thr Val Ala Pro Gly Ala Glu 2850	2855	2860
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Tyr Leu Gln Leu Gln Val Thr Glu Lys Gln Val Leu Leu Arg Ala Asp 3570	3575	3580
Asp Gly Ala Gly Glu Phe Ser Thr Ser Val Thr Arg Pro Ser Val Leu 3585	3590	3595 3600
Cys Asp Gly Gln Trp His Arg Leu Ala Val Met Lys Ser Gly Asn Val 3605	3610	3615
Leu Arg Leu Glu Val Asp Ala Gln Ser Asn His Thr Val Gly Pro Leu 3620	3625	3630
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Pro Glu Pro Met Ala Val Gln Pro Trp Pro Pro Ala Tyr Cys Gly Cys 3650	3655	3660
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Ser Asn Lys Ala His Pro Val Ser Asn Ala Ile Asp Gly Thr Glu Arg	
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Trp Trp Gln Ser Pro Pro Leu Ser Arg Gly Leu Glu Tyr Asn Glu Val	
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Ile Lys Phe Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg	
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Ser	Lys	Arg	Asp	Cys	Leu	Glu	Arg	Phe	Gly	Pro	Arg	Thr	Leu	Glu	Arg	
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cct	ggg	gcc	ttg	aac	ttc	tcc	tac	tca	ccg	tta	ctt	cga	gac	ttc	acc	528
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Lys	Ala	Thr	Asn	Ile	Arg	Leu	Arg	Phe	Leu	Arg	Thr	Asn	Thr	Leu	Leu	
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Tyr	Tyr	Tyr	Ser	Ile	Lys	Asp	Ile	Ser	Ile	Gly	Gly	Arg	Cys	Val	Cys	
		210				215					220					
cat	ggc	cac	gca	gat	gtc	tgt	gac	gcc	aag	gac	cca	ttg	gat	cct	ttc	720
His	Gly	His	Ala	Asp	Val	Cys	Asp	Ala	Lys	Asp	Pro	Leu	Asp	Pro	Phe	
225					230					235					240	
agg	ctg	cag	tgt	gcc	tgc	cag	cac	aat	aca	tgt	gga	ggc	tct	tgt	gac	768
Arg	Leu	Gln	Cys	Ala	Cys	Gln	His	Asn	Thr	Cys	Gly	Gly	Ser	Cys	Asp	
				245					250					255		
cga	tgc	tgt	cca	ggc	ttc	aac	cag	cag	ccg	tgg	aag	ccc	gcc	acc	acg	816
Arg	Cys	Cys	Pro	Gly	Phe	Asn	Gln	Gln	Pro	Trp	Lys	Pro	Ala	Thr	Thr	
			260						265				270			
gac	agc	gcc	aat	gag	tgc	cag	tcc	tgc	aat	tgc	cac	ggc	cat	gcc	tac	864
Asp	Ser	Ala	Asn	Glu	Cys	Gln	Ser	Cys	Asn	Cys	His	Gly	His	Ala	Tyr	
		275					280					285				
gac	tgt	tac	tac	gac	cct	gag	gtg	gat	cgg	cgc	aat	gcc	agc	cag	aac	912
Asp	Cys	Tyr	Tyr	Asp	Pro	Glu	Val	Asp	Arg	Arg	Asn	Ala	Ser	Gln	Asn	
		290				295					300					
cag	gac	aac	gtg	tac	cag	ggg	gga	ggg	gtc	tgc	ctg	gat	tgc	cag	cat	960
Gln	Asp	Asn	Val	Tyr	Gln	Gly	Gly	Gly	Val	Cys	Leu	Asp	Cys	Gln	His	
305					310				315						320	
cac	act	acg	ggg	atc	aac	tgt	gag	cgt	tgt	ctg	cct	ggc	ttc	ttc	cgt	1008
His	Thr	Thr	Gly	Ile	Asn	Cys	Glu	Arg	Cys	Leu	Pro	Gly	Phe	Phe	Arg	
				325					330					335		
gcc	cct	gac	cag	cct	ctc	gac	tca	cct	cat	gtc	tgt	cgg	ccc	tgc	gac	1056

Ala	Pro	Asp	Gln	Pro	Leu	Asp	Ser	Pro	His	Val	Cys	Arg	Pro	Cys	Asp		
			340					345					350				
tgt	gag	tca	gac	ttc	acg	gat	ggg	acc	tgt	gaa	gac	ttg	acg	ggc	cgc	1104	
Cys	Glu	Ser	Asp	Phe	Thr	Asp	Gly	Thr	Cys	Glu	Asp	Leu	Thr	Gly	Arg		
		355					360					365					
tgt	tac	tgc	agg	ccg	aac	ttc	aca	gga	gag	cta	tgt	gct	gcc	tgc	gct	1152	
Cys	Tyr	Cys	Arg	Pro	Asn	Phe	Thr	Gly	Glu	Leu	Cys	Ala	Ala	Cys	Ala		
	370					375					380						
gag	ggc	tac	acg	gac	ttc	cca	cac	tgc	tac	cct	ctg	cct	tca	ttt	cct	1200	
Glu	Gly	Tyr	Thr	Asp	Phe	Pro	His	Cys	Tyr	Pro	Leu	Pro	Ser	Phe	Pro		
385					390					395					400		
cac	aat	gac	acg	aga	gaa	cag	gtg	ctt	ccc	gct	gga	caa	atc	gtg	aac	1248	
His	Asn	Asp	Thr	Arg	Glu	Gln	Val	Leu	Pro	Ala	Gly	Gln	Ile	Val	Asn		
				405					410						415		
tgt	gat	tgc	aat	gct	gca	ggg	acc	cag	ggc	aat	gcc	tgc	cgg	aag	gac	1296	
Cys	Asp	Cys	Asn	Ala	Ala	Gly	Thr	Gln	Gly	Asn	Ala	Cys	Arg	Lys	Asp		
			420					425					430				
cca	agg	ttg	gga	cgg	tgt	gtc	tgc	aaa	ccc	aac	ttc	cgg	ggt	gcc	cac	1344	
Pro	Arg	Leu	Gly	Arg	Cys	Val	Cys	Lys	Pro	Asn	Phe	Arg	Gly	Ala	His		
		435					440					445					
tgt	gag	ctc	tgt	gct	cct	gga	ttc	cac	ggg	cct	agc	tgc	cac	cca	tgc	1392	
Cys	Glu	Leu	Cys	Ala	Pro	Gly	Phe	His	Gly	Pro	Ser	Cys	His	Pro	Cys		
	450					455					460						
cag	tgt	tcc	agc	cct	ggg	gta	gcc	aac	agc	ctc	tgt	gac	cca	gag	tct	1440	
Gln	Cys	Ser	Ser	Pro	Gly	Val	Ala	Asn	Ser	Leu	Cys	Asp	Pro	Glu	Ser		
465					470					475					480		
ggc	cag	tgc	atg	tgc	cgc	acc	ggc	ttt	gag	ggg	gac	agg	tgt	gac	cac	1488	
Gly	Gln	Cys	Met	Cys	Arg	Thr	Gly	Phe	Glu	Gly	Asp	Arg	Cys	Asp	His		
				485				490						495			
tgt	gcc	ctt	ggc	tat	ttc	cac	ttc	cct	ctc	tgt	cag	ctg	tgt	ggc	tgc	1536	
Cys	Ala	Leu	Gly	Tyr	Phe	His	Phe	Pro	Leu	Cys	Gln	Leu	Cys	Gly	Cys		
			500					505					510				
agc	cca	gca	ggg	acc	ctg	cct	gaa	ggc	tgt	gac	gag	gct	ggc	cgc	tgc	1584	
Ser	Pro	Ala	Gly	Thr	Leu	Pro	Glu	Gly	Cys	Asp	Glu	Ala	Gly	Arg	Cys		
		515					520					525					
cag	tgc	cga	cct	ggc	ttt	gac	ggc	cct	cac	tgt	gac	cga	tgc	ctt	cca	1632	
Gln	Cys	Arg	Pro	Gly	Phe	Asp	Gly	Pro	His	Cys	Asp	Arg	Cys	Leu	Pro		
	530					535					540						
gga	tac	cat	ggg	tat	ccc	gac	tgt	cac	gct	tgt	gcc	tgt	gac	cct	cgg	1680	
Gly	Tyr	His	Gly	Tyr	Pro	Asp	Cys	His	Ala	Cys	Ala	Cys	Asp	Pro	Arg		
545					550					555					560		
ggg	gcc	ctg	gat	caa	cag	tgt	gga	gtg	ggc	ggt	ttg	tgc	cac	tgc	cgt	1728	
Gly	Ala	Leu	Asp	Gln	Gln	Cys	Gly	Val	Gly	Gly	Leu	Cys	His	Cys	Arg		
				565				570							575		
cct	ggc	aac	aca	ggt	gcc	act	tgt	cag	gaa	tgt	agc	ccc	ggc	ttc	tac	1776	
Pro	Gly	Asn	Thr	Gly	Ala	Thr	Cys	Gln	Glu	Cys	Ser	Pro	Gly	Phe	Tyr		

580			585			590			
ggc ttc ccc agc tgc atc ccc tgc cac tgc tct gcc gat ggc tcc ttg	Gly Phe Pro Ser Cys Ile Pro Cys His Cys Ser Ala Asp Gly Ser Leu	595	600	605	1824				
cat aca acc tgt gac ccg aca acc ggc cag tgt agg tgt cga ccc cga	His Thr Thr Cys Asp Pro Thr Thr Gly Gln Cys Arg Cys Arg Pro Arg	610	615	620	1872				
gtg aca gga cta cat tgt gat atg tgt gta cca ggc gcc tat aac ttc	Val Thr Gly Leu His Cys Asp Met Cys Val Pro Gly Ala Tyr Asn Phe	625	630	635	1920				
ccc tac tgt gaa gct ggc tct tgt cat cct gct ggt ctg gcc cca gcc	Pro Tyr Cys Glu Ala Gly Ser Cys His Pro Ala Gly Leu Ala Pro Ala	645	650	655	1968				
aat cct gcc ctt cct gag aca cag gct ccc tgt atg tgc cgg gct cac	Asn Pro Ala Leu Pro Glu Thr Gln Ala Pro Cys Met Cys Arg Ala His	660	665	670	2016				
gtg gaa ggg cca agc tgt gat cgc tgt aaa cct ggg tac tgg ggg ctg	Val Glu Gly Pro Ser Cys Asp Arg Cys Lys Pro Gly Tyr Trp Gly Leu	675	680	685	2064				
agc gcc agc aac cct gaa ggc tgc aca cgc tgc agc tgt gac cca cga	Ser Ala Ser Asn Pro Glu Gly Cys Thr Arg Cys Ser Cys Asp Pro Arg	690	695	700	2112				
ggc acc ctg ggt gga gtt act gag tgc cag ggc aat ggg cag tgc ttc	Gly Thr Leu Gly Gly Val Thr Glu Cys Gln Gly Asn Gly Gln Cys Phe	705	710	715	2160				
tgc aag gct cac gtg tgt ggc aag acc tgt gca gcc tgc aag gat ggc	Cys Lys Ala His Val Cys Gly Lys Thr Cys Ala Ala Cys Lys Asp Gly	725	730	735	2208				
ttc ttt ggc ctg gat tat gct gac tac ttt ggc tgc cgt agc tgt agg	Phe Phe Gly Leu Asp Tyr Ala Asp Tyr Phe Gly Cys Arg Ser Cys Arg	740	745	750	2256				
tgt gat gtt ggt ggt gcc ctg ggt cag ggc tgt gaa cca aag aca ggt	Cys Asp Val Gly Gly Ala Leu Gly Gln Gly Cys Glu Pro Lys Thr Gly	755	760	765	2304				
gcc tgc agg tgc cgc cct aac acc caa gga ccc acc tgt agc gag cca	Ala Cys Arg Cys Arg Pro Asn Thr Gln Gly Pro Thr Cys Ser Glu Pro	770	775	780	2352				
gcg aag gac cac tac ttg cca gac ctg cac cac atg cgg ctg gaa cta	Ala Lys Asp His Tyr Leu Pro Asp Leu His His Met Arg Leu Glu Leu	785	790	795	2400				
gag gag gcg gcc act ccc gag ggc cac gct gta cgc ttt ggc ttc aac	Glu Glu Ala Ala Thr Pro Glu Gly His Ala Val Arg Phe Gly Phe Asn	805	810	815	2448				
ccc ctg gag ttt gag aac ttt agc tgg aga ggc tac gca cac atg atg	Pro Leu Glu Phe Glu Asn Phe Ser Trp Arg Gly Tyr Ala His Met Met	820	825	830	2496				

gct atc cag ccc agg att gtg gcc agg ctg aac gtg acc tcc cct gac	2544
Ala Ile Gln Pro Arg Ile Val Ala Arg Leu Asn Val Thr Ser Pro Asp	
835 840 845	
ctc ttt cga ctg gtt ttc cga tat gtc aac cgt gga tca acc agc gtg	2592
Leu Phe Arg Leu Val Phe Arg Tyr Val Asn Arg Gly Ser Thr Ser Val	
850 855 860	
aat ggg cag atc tct gtt cgt gaa gag ggc aag ctt tcc agc tgt acc	2640
Asn Gly Gln Ile Ser Val Arg Glu Glu Gly Lys Leu Ser Ser Cys Thr	
865 870 875 880	
aac tgc aca gag cag agc cag cca gtg gct ttc cca ccc agc act gag	2688
Asn Cys Thr Glu Gln Ser Gln Pro Val Ala Phe Pro Pro Ser Thr Glu	
885 890 895	
cct gcc ttt gtc act gtg ccc cag agg ggc ttt ggg gaa ccc ttt gtg	2736
Pro Ala Phe Val Thr Val Pro Gln Arg Gly Phe Gly Glu Pro Phe Val	
900 905 910	
ctg aac ccc ggc atc tgg gcc ttg ctg gtc gag gct gaa ggt gta ctc	2784
Leu Asn Pro Gly Ile Trp Ala Leu Leu Val Glu Ala Glu Gly Val Leu	
915 920 925	
ttg gac tac gtg gtc cta ctg ccc agc acc tac tat gag gca gct ctc	2832
Leu Asp Tyr Val Val Leu Leu Pro Ser Thr Tyr Tyr Glu Ala Ala Leu	
930 935 940	
cta cag cat cga gta acg gag gcc tgt acc tac cgt ccc tca gcc ctg	2880
Leu Gln His Arg Val Thr Glu Ala Cys Thr Tyr Arg Pro Ser Ala Leu	
945 950 955 960	
cac tcc aca gag aac tgt ctt gtc tat gct cac cta ccc ctg gat ggc	2928
His Ser Thr Glu Asn Cys Leu Val Tyr Ala His Leu Pro Leu Asp Gly	
965 970 975	
ttc cct tca gca gct gga act gag gcc ctg tgt cgc cat gac aac agc	2976
Phe Pro Ser Ala Ala Gly Thr Glu Ala Leu Cys Arg His Asp Asn Ser	
980 985 990	
ctg ccc cgg ccc tgc ccc aca gag cag ctc agc ccc tca cac cca ccg	3024
Leu Pro Arg Pro Cys Pro Thr Glu Gln Leu Ser Pro Ser His Pro Pro	
995 1000 1005	
ctg gcg acc tgc ttc ggc agt gat gtg gac atc cag ctc gag atg gcc	3072
Leu Ala Thr Cys Phe Gly Ser Asp Val Asp Ile Gln Leu Glu Met Ala	
1010 1015 1020	
gtg cct cag cct ggc caa tat gtt ctc gtg gtg gaa tat gtc ggt gag	3120
Val Pro Gln Pro Gly Gln Tyr Val Leu Val Val Glu Tyr Val Gly Glu	
1025 1030 1035 1040	
gat tca cac caa gag atg gga gtg gct gtg cac acc cct cag aga gcc	3168
Asp Ser His Gln Glu Met Gly Val Ala Val His Thr Pro Gln Arg Ala	
1045 1050 1055	
ccc cag caa ggg gtg ctc aac ctc cac ccc tgc cca tac agc tcc ctg	3216
Pro Gln Gln Gly Val Leu Asn Leu His Pro Cys Pro Tyr Ser Ser Leu	
1060 1065 1070	

tgc cgg agt ccg gct cgg gac acc cag cat cat cta gcc atc ttc cac	3264
Cys Arg Ser Pro Ala Arg Asp Thr Gln His His Leu Ala Ile Phe His	
1075 1080 1085	
ctg gac tct gag gct agc atc cgg ctc aca gct gag caa gct cac ttc	3312
Leu Asp Ser Glu Ala Ser Ile Arg Leu Thr Ala Glu Gln Ala His Phe	
1090 1095 1100	
ttc ctg cac agc gtc acc ctg gta cct gtg gag gag ttc agt act gag	3360
Phe Leu His Ser Val Thr Leu Val Pro Val Glu Glu Phe Ser Thr Glu	
1105 1110 1115 1120	
ttt gtg gag ccc cgg gtc ttc tgt gtg agc agt cat gga act ttc aac	3408
Phe Val Glu Pro Arg Val Phe Cys Val Ser Ser His Gly Thr Phe Asn	
1125 1130 1135	
ccc agc agt gct gcc tgt cta gcc tcc cga ttc ccg aag cca ccg cag	3456
Pro Ser Ser Ala Ala Cys Leu Ala Ser Arg Phe Pro Lys Pro Pro Gln	
1140 1145 1150	
ccc atc atc ctt aag gac tgc cag gtc ttg ccg ctg cct ccc gac ctg	3504
Pro Ile Ile Leu Lys Asp Cys Gln Val Leu Pro Leu Pro Pro Asp Leu	
1155 1160 1165	
cct ctg act cag tct cag gag ctc tca cca ggt gca ccc ccc gag gga	3552
Pro Leu Thr Gln Ser Gln Glu Leu Ser Pro Gly Ala Pro Pro Glu Gly	
1170 1175 1180	
cca cag cct cgg ccg cca act gcg gtg gat cct aat gca gaa ccc acc	3600
Pro Gln Pro Arg Pro Pro Thr Ala Val Asp Pro Asn Ala Glu Pro Thr	
1185 1190 1195 1200	
ttg ctg cgc cac ccc cag ggc acg gtg gtc ttc acc acc cag gtg ccc	3648
Leu Leu Arg His Pro Gln Gly Thr Val Val Phe Thr Thr Gln Val Pro	
1205 1210 1215	
acc ctg ggc cgc tat gcc ttc ctg ctg cac ggc tac cag ccg gtc cac	3696
Thr Leu Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro Val His	
1220 1225 1230	
ccc tcc ttc cct gtg gag gta ctc att aat ggt ggc cgc atc tgg cag	3744
Pro Ser Phe Pro Val Glu Val Leu Ile Asn Gly Gly Arg Ile Trp Gln	
1235 1240 1245	
ggc cac gcc aac gcc agc ttt tgt cct cat ggt tat ggc tgc cgt acc	3792
Gly His Ala Asn Ala Ser Phe Cys Pro His Gly Tyr Gly Cys Arg Thr	
1250 1255 1260	
ctg gtg ttg tgt gag ggt cag acg atg ctg gat gtt aca gac aac gag	3840
Leu Val Leu Cys Glu Gly Gln Thr Met Leu Asp Val Thr Asp Asn Glu	
1265 1270 1275 1280	
ctc acc gtg act gtg cgt gtg cca gaa ggc cgg tgg ctc tgg ctg gac	3888
Leu Thr Val Thr Val Arg Val Pro Glu Gly Arg Trp Leu Trp Leu Asp	
1285 1290 1295	
tac gta ctc att gtc cct gag gat gct tac agc tcc agt tac ctc caa	3936
Tyr Val Leu Ile Val Pro Glu Asp Ala Tyr Ser Ser Ser Tyr Leu Gln	
1300 1305 1310	
gag gag cct ttg gac aaa tcc tat gac ttc atc agc cac tgt gcc acc	3984

Glu	Glu	Pro	Leu	Asp	Lys	Ser	Tyr	Asp	Phe	Ile	Ser	His	Cys	Ala	Thr		
		1315					1320					1325					
cag	ggc	tac	cac	att	agc	ccc	agc	agc	tca	tct	cca	ttc	tgc	cg	aat	4032	
Gln	Gly	Tyr	His	Ile	Ser	Pro	Ser	Ser	Ser	Ser	Pro	Phe	Cys	Arg	Asn		
	1330					1335					1340						
gcc	gcc	acc	tcc	ttg	tct	ctc	ttc	tac	aac	aac	ggg	gcc	ctc	cct	tgt	4080	
Ala	Ala	Thr	Ser	Leu	Ser	Leu	Phe	Tyr	Asn	Asn	Gly	Ala	Leu	Pro	Cys		
1345					1350					1355					1360		
ggc	tgc	cac	gag	gtg	ggt	gcc	gta	agc	ccc	acg	tgc	gaa	ccc	ttc	ggg	4128	
Gly	Cys	His	Glu	Val	Gly	Ala	Val	Ser	Pro	Thr	Cys	Glu	Pro	Phe	Gly		
			1365					1370						1375			
ggc	cag	tgt	ccc	tgc	cg	ggc	cac	g	att	ggc	cgt	gac	tgt	tcc	cg	4176	
Gly	Gln	Cys	Pro	Cys	Arg	Gly	His	Val	Ile	Gly	Arg	Asp	Cys	Ser	Arg		
			1380					1385						1390			
tgt	gcc	acc	ggc	tac	tgg	ggt	ttc	ccc	aac	tgc	agg	ccc	tgt	gac	tgt	4224	
Cys	Ala	Thr	Gly	Tyr	Trp	Gly	Phe	Pro	Asn	Cys	Arg	Pro	Cys	Asp	Cys		
		1395					1400						1405				
gga	gcc	cg	ctg	tgt	gac	gag	ctc	acg	ggc	cag	tgt	atc	tgt	cca	cca	4272	
Gly	Ala	Arg	Leu	Cys	Asp	Glu	Leu	Thr	Gly	Gln	Cys	Ile	Cys	Pro	Pro		
	1410						1415					1420					
cg	act	g	ccc	cct	gac	tgc	ttg	gtc	tgc	cag	cca	cag	agc	ttt	ggt	4320	
Arg	Thr	Val	Pro	Pro	Asp	Cys	Leu	Val	Cys	Gln	Pro	Gln	Ser	Phe	Gly		
1425					1430					1435					1440		
tgc	cac	ccc	ttg	gtg	ggc	tgt	gag	gag	tgt	aac	tgc	tca	ggg	ccc	ggc	4368	
Cys	His	Pro	Leu	Val	Gly	Cys	Glu	Glu	Cys	Asn	Cys	Ser	Gly	Pro	Gly		
			1445						1450					1455			
gtc	cag	gag	ctg	acg	gac	cct	acc	tgt	gac	atg	gac	agc	ggc	cag	tgc	4416	
Val	Gln	Glu	Leu	Thr	Asp	Pro	Thr	Cys	Asp	Met	Asp	Ser	Gly	Gln	Cys		
			1460					1465						1470			
aga	tgc	aga	ccc	aat	gta	gct	gga	cgt	cg	tgt	gat	acc	tgt	gcc	ccg	4464	
Arg	Cys	Arg	Pro	Asn	Val	Ala	Gly	Arg	Arg	Cys	Asp	Thr	Cys	Ala	Pro		
		1475					1480						1485				
ggc	ttc	tat	ggc	tat	cct	agc	tgt	cg	ccc	tgt	gac	tgc	cat	gag	gca	4512	
Gly	Phe	Tyr	Gly	Tyr	Pro	Ser	Cys	Arg	Pro	Cys	Asp	Cys	His	Glu	Ala		
	1490					1495						1500					
ggc	acc	atg	gct	agc	gtg	tgt	gac	ccc	ctc	aca	ggc	caa	tgc	cat	tgc	4560	
Gly	Thr	Met	Ala	Ser	Val	Cys	Asp	Pro	Leu	Thr	Gly	Gln	Cys	His	Cys		
1505					1510					1515					1520		
aag	gag	aac	gtg	cag	ggc	tca	aga	tgt	gac	cag	tgt	cg	gtg	ggg	acc	4608	
Lys	Glu	Asn	Val	Gln	Gly	Ser	Arg	Cys	Asp	Gln	Cys	Arg	Val	Gly	Thr		
			1525					1530						1535			
ttc	tcc	ttg	gat	gct	gct	aac	ccc	aag	ggc	tgt	acc	cg	tgc	ttc	tgt	4656	
Phe	Ser	Leu	Asp	Ala	Ala	Asn	Pro	Lys	Gly	Cys	Thr	Arg	Cys	Phe	Cys		
			1540					1545						1550			
ttc	ggg	gcc	aca	gag	cg	tgt	ggg	aac	tct	aac	ctc	gcc	cg	cat	gag	4704	
Phe	Gly	Ala	Thr	Glu	Arg	Cys	Gly	Asn	Ser	Asn	Leu	Ala	Arg	His	Glu		

1555	1560	1565	
ttc gtg gac atg gag ggc tgg gtg ctg ttg agc agt gac cgg cag gtg Phe Val Asp Met Glu Gly Trp Val Leu Leu Ser Ser Asp Arg Gln Val 1570	1575	1580	4752
gta ccc cac gag cat cgg cct gag ata gag ctg ctg cac gca gat ctg Val Pro His Glu His Arg Pro Glu Ile Glu Leu Leu His Ala Asp Leu 1585	1590	1595	4800
cgc tct gtg gct gac act ttc tca gag ctg tac tgg cag gct ccg ccc Arg Ser Val Ala Asp Thr Phe Ser Glu Leu Tyr Trp Gln Ala Pro Pro 1605	1610	1615	4848
tcc tat ctg gga gac agg gtg tca tcc tac ggt gga acc ctc cac tat Ser Tyr Leu Gly Asp Arg Val Ser Ser Tyr Gly Gly Thr Leu His Tyr 1620	1625	1630	4896
gag ctg cac tca gag acc cag cga ggt gat atc ttc att ccc tac gag Glu Leu His Ser Glu Thr Gln Arg Gly Asp Ile Phe Ile Pro Tyr Glu 1635	1640	1645	4944
agc cgg ccg gac gtc gtg ctg cag ggc aac caa atg agc atc gcc ttc Ser Arg Pro Asp Val Val Leu Gln Gly Asn Gln Met Ser Ile Ala Phe 1650	1655	1660	4992
ctg gaa ctg gcg tac cct ccg cct ggc cag gtt cac cga gga cag cta Leu Glu Leu Ala Tyr Pro Pro Gly Gln Val His Arg Gly Gln Leu 1665	1670	1675	5040
cag ctg gta gag ggg aac ttc cgg cac ttg gag act cac aac ccc gtg Gln Leu Val Glu Gly Asn Phe Arg His Leu Glu Thr His Asn Pro Val 1685	1690	1695	5088
tcc cga gaa gaa ctc atg atg gtg ctg gcc ggc ctg gag cag ctg cag Ser Arg Glu Glu Leu Met Met Val Leu Ala Gly Leu Glu Gln Leu Gln 1700	1705	1710	5136
atc cgt gct ctc ttc tcg cag acc tct tcc agt gtc tcc ttg cgt aga Ile Arg Ala Leu Phe Ser Gln Thr Ser Ser Ser Val Ser Leu Arg Arg 1715	1720	1725	5184
gtg gta ctg gag gtg gct agc gag gct ggt agg ggg cct cca gcc agc Val Val Leu Glu Val Ala Ser Glu Ala Gly Arg Gly Pro Pro Ala Ser 1730	1735	1740	5232
aat gtg gaa ctg tgt atg tgc cct gcc aac tac cgt ggg gac tcg tgc Asn Val Glu Leu Cys Met Cys Pro Ala Asn Tyr Arg Gly Asp Ser Cys 1745	1750	1755	5280
cag gaa tgt gcc cct ggc tat tac cgg gac acc aag ggt ctc ttc cta Gln Glu Cys Ala Pro Gly Tyr Tyr Arg Asp Thr Lys Gly Leu Phe Leu 1765	1770	1775	5328
ggc cga tgt gtc ccc tgt cag tgc cat ggc cat tca gat cgc tgc ctt Gly Arg Cys Val Pro Cys Gln Cys His Gly His Ser Asp Arg Cys Leu 1780	1785	1790	5376
cct ggc tct ggc att tgt gtg ggc tgc cag cac aac aca gaa ggg gac Pro Gly Ser Gly Ile Cys Val Gly Cys Gln His Asn Thr Glu Gly Asp 1795	1800	1805	5424

caa tgt gag cgc tgt agg cct ggc ttt gtc agc agt gat ccc agt aac 5472
 Gln Cys Glu Arg Cys Arg Pro Gly Phe Val Ser Ser Asp Pro Ser Asn
 1810 1815 1820

cct gca tcc cca tgt gtg agc tgc cct tgc ccc ttg gca gtg ccc tcc 5520
 Pro Ala Ser Pro Cys Val Ser Cys Pro Cys Pro Leu Ala Val Pro Ser
 1825 1830 1835 1840

aat aat ttt gca gac ggt tgc gtc tta aga aat ggc cga acc cag tgc 5568
 Asn Asn Phe Ala Asp Gly Cys Val Leu Arg Asn Gly Arg Thr Gln Cys
 1845 1850 1855

ctc tgc agg cca ggc tat gct ggt gcc tcc tgc gag cgg tgt gca cct 5616
 Leu Cys Arg Pro Gly Tyr Ala Gly Ala Ser Cys Glu Arg Cys Ala Pro
 1860 1865 1870

ggc ttt ttt ggg aac ccc ctg gtg cta ggc agc tcc tgt cag ccc tgc 5664
 Gly Phe Phe Gly Asn Pro Leu Val Leu Gly Ser Ser Cys Gln Pro Cys
 1875 1880 1885

gac tgc agc ggt aat gga gac ccc aac atg atc ttc agt gac tgc gac 5712
 Asp Cys Ser Gly Asn Gly Asp Pro Asn Met Ile Phe Ser Asp Cys Asp
 1890 1895 1900

ccc ctg acg ggt gcc tgt cga ggc tgc ctc cgt cac acc act ggg ccc 5760
 Pro Leu Thr Gly Ala Cys Arg Gly Cys Leu Arg His Thr Thr Gly Pro
 1905 1910 1915 1920

cac tgt gaa cgc tgt gcc cca ggc ttc tat ggc aat gct ttg ttg cca 5808
 His Cys Glu Arg Cys Ala Pro Gly Phe Tyr Gly Asn Ala Leu Leu Pro
 1925 1930 1935

ggc aac tgc acc cgg tgt gac tgt tcc cca tgt ggg aca gaa acc tgt 5856
 Gly Asn Cys Thr Arg Cys Asp Cys Ser Pro Cys Gly Thr Glu Thr Cys
 1940 1945 1950

gat ccc cag agt gga cgc tgc ctg tgc aaa gca ggc gtg act gga caa 5904
 Asp Pro Gln Ser Gly Arg Cys Leu Cys Lys Ala Gly Val Thr Gly Gln
 1955 1960 1965

cgt tgt gac cgc tgt ttg gaa gga tac ttc ggt ttt gag caa tgc cag 5952
 Arg Cys Asp Arg Cys Leu Glu Gly Tyr Phe Gly Phe Glu Gln Cys Gln
 1970 1975 1980

ggc tgc cgc cct tgt gcc tgt gga cca gct gcc aag ggc tcc gag tgc 6000
 Gly Cys Arg Pro Cys Ala Cys Gly Pro Ala Ala Lys Gly Ser Glu Cys
 1985 1990 1995 2000

cac cct cag agc ggt cag tgt cac tgc cag cca ggg acc aca gga ccc 6048
 His Pro Gln Ser Gly Gln Cys His Cys Gln Pro Gly Thr Thr Gly Pro
 2005 2010 2015

cag tgc ctc gag tgc gcc cct ggc tac tgg ggc ctc cca gag aag ggc 6096
 Gln Cys Leu Glu Cys Ala Pro Gly Tyr Trp Gly Leu Pro Glu Lys Gly
 2020 2025 2030

tgc agg cgc tgc cag tgt ccc cga ggc cac tgt gac cca cac acg ggc 6144
 Cys Arg Arg Cys Gln Cys Pro Arg Gly His Cys Asp Pro His Thr Gly
 2035 2040 2045

cac tgc acc tgt ccc ccg ggg ctc agc ggg gaa cgc tgt gac acc tgc His Cys Thr Cys Pro Pro Gly Leu Ser Gly Glu Arg Cys Asp Thr Cys 2050 2055 2060	6192
agc cag cag cac cag gtg cct gta ccg ggc aag cct ggg ggc cat ggc Ser Gln Gln His Gln Val Pro Val Pro Gly Lys Pro Gly Gly His Gly 2065 2070 2075 2080	6240
ata cac tgt gaa gtg tgt gac cac tgt gtg gtt ctc ctt ctg gat gac Ile His Cys Glu Val Cys Asp His Cys Val Val Leu Leu Leu Asp Asp 2085 2090 2095	6288
ctc gag cgg gct ggt gcc ctc ctc ccc gct atc cgt gag cag ctg cag Leu Glu Arg Ala Gly Ala Leu Leu Pro Ala Ile Arg Glu Gln Leu Gln 2100 2105 2110	6336
ggt atc aat gcc agc tcc gcg gcc tgg gcc agg ctg cac agg ctg aat Gly Ile Asn Ala Ser Ser Ala Ala Trp Ala Arg Leu His Arg Leu Asn 2115 2120 2125	6384
gcc tcc att gct gac ctg cag agt aaa ctc cgg agg cca ccg gga ccc Ala Ser Ile Ala Asp Leu Gln Ser Lys Leu Arg Arg Pro Pro Gly Pro 2130 2135 2140	6432
cgc tac cag gca gca cag cag cta cag act cta gag cag cag agt ata Arg Tyr Gln Ala Ala Gln Gln Leu Gln Thr Leu Glu Gln Gln Ser Ile 2145 2150 2155 2160	6480
agc ctt caa cag gac acg gag agg ctg ggc agt cag gcc aca ggg gtc Ser Leu Gln Gln Asp Thr Glu Arg Leu Gly Ser Gln Ala Thr Gly Val 2165 2170 2175	6528
caa ggt cag gca ggc cag cta ctg gac acc aca gag tcc aca ctg ggc Gln Gly Gln Ala Gly Gln Leu Leu Asp Thr Thr Glu Ser Thr Leu Gly 2180 2185 2190	6576
cgg gca cag aag ttg ttg gag tct gtg cga gct gtg ggc cgt gcc ctg Arg Ala Gln Lys Leu Leu Glu Ser Val Arg Ala Val Gly Arg Ala Leu 2195 2200 2205	6624
aat gag ctg gca tct cgc atg ggc caa gga tct cca ggc gat gcc ttg Asn Glu Leu Ala Ser Arg Met Gly Gln Gly Ser Pro Gly Asp Ala Leu 2210 2215 2220	6672
gta ccg tct ggc gag cag ctg cgc tgg gct ctg gct gaa gtg gag cgg Val Pro Ser Gly Glu Gln Leu Arg Trp Ala Leu Ala Glu Val Glu Arg 2225 2230 2235 2240	6720
ctg ctc tgg gat atg cgg acg cgt gac ctg ggg gcc cag ggg gca gtg Leu Leu Trp Asp Met Arg Thr Arg Asp Leu Gly Ala Gln Gly Ala Val 2245 2250 2255	6768
gca gag gcc gaa ctg gcc gaa gcc cag agg ctg atg gct cgt gtc cag Ala Glu Ala Glu Leu Ala Glu Ala Gln Arg Leu Met Ala Arg Val Gln 2260 2265 2270	6816
gag cag ctg acc agc ttc tgg gag gag aac cag tca ttg gcc aca cac Glu Gln Leu Thr Ser Phe Trp Glu Glu Asn Gln Ser Leu Ala Thr His 2275 2280 2285	6864
att cgg gac cag ctg gct cag tat gag tct ggc ctc atg gat ctt cgt	6912

Ile Arg Asp Gln Leu Ala Gln Tyr Glu Ser Gly Leu Met Asp Leu Arg	
2290	2295 2300
gag gcc ctg aac cag gcc gtt aat acc acc cgg gag gct gag gaa ctc	6960
Glu Ala Leu Asn Gln Ala Val Asn Thr Thr Arg Glu Ala Glu Glu Leu	
2305	2310 2315 2320
aac agc cgc aac cag gaa cgg gtg aag gaa gcc ctg caa tgg aaa cag	7008
Asn Ser Arg Asn Gln Glu Arg Val Lys Glu Ala Leu Gln Trp Lys Gln	
	2325 2330 2335
gaa ctg tcc cag gac aat gcc acc ctg aag gcc act ctt caa gct gcc	7056
Glu Leu Ser Gln Asp Asn Ala Thr Leu Lys Ala Thr Leu Gln Ala Ala	
	2340 2345 2350
agt ctc atc ttg ggc cat gtt tct gag ctt ctg cag ggc ata gac cag	7104
Ser Leu Ile Leu Gly His Val Ser Glu Leu Leu Gln Gly Ile Asp Gln	
	2355 2360 2365
gct aag gag gac cta gag cac ctg gcg gcc agc ctg gat gga gcc tgg	7152
Ala Lys Glu Asp Leu Glu His Leu Ala Ala Ser Leu Asp Gly Ala Trp	
	2370 2375 2380
aca ccc tta ctg aag agg atg cag gcc ttt tcc cct gcc agc agc aag	7200
Thr Pro Leu Leu Lys Arg Met Gln Ala Phe Ser Pro Ala Ser Ser Lys	
2385	2390 2395 2400
gtg gac ttg gta gag gct gct gag gcc cac gct cag aag ctg aac cag	7248
Val Asp Leu Val Glu Ala Ala Glu Ala His Ala Gln Lys Leu Asn Gln	
	2405 2410 2415
ctg gca atc aac ctg tct ggc atc atc ctt ggc atc aat cag gac cgc	7296
Leu Ala Ile Asn Leu Ser Gly Ile Ile Leu Gly Ile Asn Gln Asp Arg	
	2420 2425 2430
ttc atc cag agg gct gtg gaa gcc tcc aat gcc tac agc agc atc ctt	7344
Phe Ile Gln Arg Ala Val Glu Ala Ser Asn Ala Tyr Ser Ser Ile Leu	
	2435 2440 2445
cag gcc gtt cag gct gcc gag gat gcg gca ggc cag gca ctg agg cag	7392
Gln Ala Val Gln Ala Ala Glu Asp Ala Ala Gly Gln Ala Leu Arg Gln	
	2450 2455 2460
gcc agc cgc aca tgg gag atg gtg gtg cag cgg ggc cta gca gct gga	7440
Ala Ser Arg Thr Trp Glu Met Val Val Gln Arg Gly Leu Ala Ala Gly	
2465	2470 2475 2480
gcc cgg cag ctg tta gcc aac agc agt gcc ctg gag gag acc atc ctt	7488
Ala Arg Gln Leu Leu Ala Asn Ser Ser Ala Leu Glu Glu Thr Ile Leu	
	2485 2490 2495
gga cac cag ggg agg ctg ggc ctt gct cag ggc cgt ctg cag gct gcg	7536
Gly His Gln Gly Arg Leu Gly Leu Ala Gln Gly Arg Leu Gln Ala Ala	
	2500 2505 2510
ggg atc cag ctt cat aat gtc tgg gcc agg aag aac cag cta gca gcc	7584
Gly Ile Gln Leu His Asn Val Trp Ala Arg Lys Asn Gln Leu Ala Ala	
	2515 2520 2525
cag atc cag gag gca caa gcc atg ctg gcc atg gac acg agc gag acc	7632
Gln Ile Gln Glu Ala Gln Ala Met Leu Ala Met Asp Thr Ser Glu Thr	

2530	2535	2540	
agt gag aag att gct cac gcc aag gct gtg gct gcc gaa gcc ctc agt			7680
Ser Glu Lys Ile Ala His Ala Lys Ala Val Ala Ala Glu Ala Leu Ser			
2545	2550	2555	2560
acg gcc acc cac gtg cag tct cag ctt cag ggt atg cag aag aat gtg			7728
Thr Ala Thr His Val Gln Ser Gln Leu Gln Gly Met Gln Lys Asn Val			
	2565	2570	2575
gag agg tgg cag agc cag ctg gga ggc ctg caa ggc cag gac ctg agc			7776
Glu Arg Trp Gln Ser Gln Leu Gly Gly Leu Gln Gly Gln Asp Leu Ser			
	2580	2585	2590
cag gtg gaa cgg gat gca agc agt tca gtg tcc acc ctg gag aag aca			7824
Gln Val Glu Arg Asp Ala Ser Ser Ser Val Ser Thr Leu Glu Lys Thr			
	2595	2600	2605
ttg cca cag ctg ctg gcc aaa ctg agc cgt cta gag aac cgt gga gtt			7872
Leu Pro Gln Leu Leu Ala Lys Leu Ser Arg Leu Glu Asn Arg Gly Val			
	2610	2615	2620
cac aat gcc agc ctg gct ttg tct gcc aac att ggt cgt gtg cgc aag			7920
His Asn Ala Ser Leu Ala Leu Ser Ala Asn Ile Gly Arg Val Arg Lys			
2625	2630	2635	2640
ctc att gcc caa gcc cgg agt gcc gcc agc aag gtc aag gtg tcc atg			7968
Leu Ile Ala Gln Ala Arg Ser Ala Ala Ser Lys Val Lys Val Ser Met			
	2645	2650	2655
aag ttc aat ggg cgt tca ggg gta cga ctg cgt ccc cca cga gac ctt			8016
Lys Phe Asn Gly Arg Ser Gly Val Arg Leu Arg Pro Pro Arg Asp Leu			
	2660	2665	2670
gcc gac ctt gct gcg tac act gcc ctc aag ttc cac atc cag agc cca			8064
Ala Asp Leu Ala Ala Tyr Thr Ala Leu Lys Phe His Ile Gln Ser Pro			
	2675	2680	2685
gtg cca gcg ccc gaa cct ggc aag aac acg ggg gac cac ttt gtt ctg			8112
Val Pro Ala Pro Glu Pro Gly Lys Asn Thr Gly Asp His Phe Val Leu			
	2690	2695	2700
tac atg ggc agc cgc cag gcc act ggg gac tac atg gga gtg tct ctg			8160
Tyr Met Gly Ser Arg Gln Ala Thr Gly Asp Tyr Met Gly Val Ser Leu			
2705	2710	2715	2720
cgt aat cag aag gtg cac tgg gtg tac agg cta gga aag gct ggc ccc			8208
Arg Asn Gln Lys Val His Trp Val Tyr Arg Leu Gly Lys Ala Gly Pro			
	2725	2730	2735
aca act ctc agc atc gac gag aac atc ggg gag cag ttt gca gcc gtc			8256
Thr Thr Leu Ser Ile Asp Glu Asn Ile Gly Glu Gln Phe Ala Ala Val			
	2740	2745	2750
agc atc gac agg acc ctc cag ttt ggc cac atg tot gtc acc gtg gag			8304
Ser Ile Asp Arg Thr Leu Gln Phe Gly His Met Ser Val Thr Val Glu			
	2755	2760	2765
aaa cag atg gtt cat gag atc aag gga gac acg gtg gcc cct ggg agc			8352
Lys Gln Met Val His Glu Ile Lys Gly Asp Thr Val Ala Pro Gly Ser			
	2770	2775	2780

gag gga cta ctc aac ctg cat cct gac gat ttt gtc ttc tac gtg gga Glu Gly Leu Leu Asn Leu His Pro Asp Asp Phe Val Phe Tyr Val Gly 2785 2790 2795 2800	8400
gga tac ccc agc aac ttc acg ccc cct gaa ccc ctc cga ttc cct ggc Gly Tyr Pro Ser Asn Phe Thr Pro Pro Glu Pro Leu Arg Phe Pro Gly 2805 2810 2815	8448
tac ctg ggc tgc att gag atg gaa aca ctg aat gag gag gtg gtc agc Tyr Leu Gly Cys Ile Glu Met Glu Thr Leu Asn Glu Glu Val Val Ser 2820 2825 2830	8496
ctc tac aat ttt gag cag acc ttc atg ctg gac acg gca gta gat aaa Leu Tyr Asn Phe Glu Gln Thr Phe Met Leu Asp Thr Ala Val Asp Lys 2835 2840 2845	8544
cct tgt gct cgc tcc aag gcc acc ggt gac cca tgg ctc aca gat ggc Pro Cys Ala Arg Ser Lys Ala Thr Gly Asp Pro Trp Leu Thr Asp Gly 2850 2855 2860	8592
tcc tac ctg gat ggc agt ggc ttt gcc cgc atc agc ttt gag aag cag Ser Tyr Leu Asp Gly Ser Gly Phe Ala Arg Ile Ser Phe Glu Lys Gln 2865 2870 2875 2880	8640
ttc agc aac aca aaa cgc ttt gac cag gag ctg cgg ctt gtg tcc tac Phe Ser Asn Thr Lys Arg Phe Asp Gln Glu Leu Arg Leu Val Ser Tyr 2885 2890 2895	8688
aat ggg atc atc ttt ttc ctc aag caa gag agc cag ttc ttg tgc ctg Asn Gly Ile Ile Phe Phe Leu Lys Gln Glu Ser Gln Phe Leu Cys Leu 2900 2905 2910	8736
gca gtg cag gaa ggc acc ctg gtg ctc ttc tat gac ttc ggc tct ggc Ala Val Gln Glu Gly Thr Leu Val Leu Phe Tyr Asp Phe Gly Ser Gly 2915 2920 2925	8784
ctg aag aag gcc gac cca ctg cag ccc cca caa gcc ttg acg gca gcc Leu Lys Lys Ala Asp Pro Leu Gln Pro Pro Gln Ala Leu Thr Ala Ala 2930 2935 2940	8832
agc aag gcg atc caa gtg ttt cta ttg gct ggc aat cgc aaa cgt gtg Ser Lys Ala Ile Gln Val Phe Leu Leu Ala Gly Asn Arg Lys Arg Val 2945 2950 2955 2960	8880
ttg gtg cgt gtg gag cgg gcc act gtg ttc agc gta gac cag gat aac Leu Val Arg Val Glu Arg Ala Thr Val Phe Ser Val Asp Gln Asp Asn 2965 2970 2975	8928
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cag ctg ccc ttg agc cta cgg cag ctc ttc ccc tcc gga ggc tct gtc Gln Leu Pro Leu Ser Leu Arg Gln Leu Phe Pro Ser Gly Gly Ser Val 2995 3000 3005	9024
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 Lys Arg Leu Asn Thr Thr Gly Ile Ser Phe Gly Cys Thr Ala Asp Leu
 3025 3030 3035 3040

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 Leu Val Gly Arg Thr Met Thr Phe His Gly His Gly Phe Leu Pro Leu
 3045 3050 3055

 gca ctt cct gat gtg gca ccc atc acc gaa gtg gtc tat tct ggc ttt 9216
 Ala Leu Pro Asp Val Ala Pro Ile Thr Glu Val Val Tyr Ser Gly Phe
 3060 3065 3070

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 Gly Phe Arg Gly Thr Gln Asp Asn Asn Leu Leu Tyr Tyr Arg Thr Ser
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 ccg gat ggg ccg tac cag gta tcc ctg agg gag ggc cac gtg aca ctc 9312
 Pro Asp Gly Pro Tyr Gln Val Ser Leu Arg Glu Gly His Val Thr Leu
 3090 3095 3100

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 Arg Phe Met Asn Gln Glu Val Glu Thr Gln Arg Val Phe Ala Asp Gly
 3105 3110 3115 3120

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 Ala Pro His Tyr Val Ala Phe Tyr Ser Asn Val Thr Gly Val Trp Leu
 3125 3130 3135

 tat gtg gat gac cag cta caa cta gta aag tct cat gag aga aca act 9456
 Tyr Val Asp Asp Gln Leu Gln Leu Val Lys Ser His Glu Arg Thr Thr
 3140 3145 3150

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 Pro Met Leu Gln Leu Gln Pro Glu Glu Pro Ser Arg Leu Leu Leu Gly
 3155 3160 3165

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 Gly Leu Pro Val Ser Gly Thr Phe His Asn Phe Ser Gly Cys Ile Ser
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 Gln Leu Ile Glu Thr Ser Arg Ala Thr Ala Gln Lys Val Ser Arg Arg
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 Ser Arg Gln Pro Ser Gln Asp Leu Ala Cys Thr Thr Pro Trp Leu Pro
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 3265 3270 3275 3280

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 Ser Met Leu Val Arg Pro His Ala Ala Ser Gln Gly Leu Leu Leu Ser
 3285 3290 3295

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 Thr Ala Pro Met Ser Gly Arg Ser Pro Ser Leu Val Leu Phe Leu Asn
 3300 3305 3310

cat gga cac ttt gtc gca cag act gag ggc cct ggg ccc cgg ctc cag 9984
 His Gly His Phe Val Ala Gln Thr Glu Gly Pro Gly Pro Arg Leu Gln
 3315 3320 3325

gtc cag agt cgc cag cac tca cgg gct ggc cag tgg cac agg gtg tcc 10032
 Val Gln Ser Arg Gln His Ser Arg Ala Gly Gln Trp His Arg Val Ser
 3330 3335 3340

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 Val Arg Trp Gly Met Gln Gln Ile Gln Leu Val Val Asp Gly Ser Gln
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acc tgg agc cag aag gct ctc cac cat cgg gtc ccc agg gca gag cga 10128
 Thr Trp Ser Gln Lys Ala Leu His His Arg Val Pro Arg Ala Glu Arg
 3365 3370 3375

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 Ser Ser Lys Leu Pro Val Ser Val Gly Phe Ser Gly Cys Leu Lys Lys
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 Ile Phe His Leu Gly Gln Ala Leu Ala Thr Pro Tyr Met Gln Leu Lys
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 3490 3495 3500

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Thr Gln Ser Asn His Thr Thr Gly Arg Leu Pro Glu Ser Leu Ala Gly				
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Ser Pro Ala Leu Leu His Leu Gly Ser Leu Pro Lys Ser Ser Thr Ala				
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Arg Pro Glu Leu Pro Ala Tyr Arg Gly Cys Leu Arg Lys Leu Leu Ile				
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Val Gly Met Arg Gly Cys Pro Ser Gly Thr Leu Ala Leu Ser Lys Gln				
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Gly Lys Ala Leu Thr Gln Arg His Ala Lys Pro Ser Val Ser Pro Leu				
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ctt tgg cat tgagggttcc cagaccttgg ggtttgctta cactttctat				10945
Leu Trp His				
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atat				11009
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Asn Gln Thr Ile Gln Gly Gln Tyr Cys Asp Ile Cys Thr Ala Ala Asn				
	20	25	30	
Ser Asn Lys Ala His Pro Val Ser Asn Ala Ile Asp Gly Thr Glu Arg				
	35	40	45	
Trp Trp Gln Ser Pro Pro Leu Ser Arg Gly Leu Glu Tyr Asn Glu Val				
	50	55	60	
Asn Val Thr Leu Asp Leu Gly Gln Val Phe His Val Ala Tyr Val Leu				
	65	70	75	80
Ile Lys Phe Ala Asn Ser Pro Arg Pro Asp Leu Trp Val Leu Glu Arg				

				85					90					95			
Ser	Thr	Asp	Phe	Gly	His	Thr	Tyr	Gln	Pro	Trp	Gln	Phe	Phe	Ala	Ser		
			100					105						110			
Ser	Lys	Arg	Asp	Cys	Leu	Glu	Arg	Phe	Gly	Pro	Arg	Thr	Leu	Glu	Arg		
		115					120					125					
Ile	Thr	Gln	Asp	Asp	Asp	Val	Ile	Cys	Thr	Thr	Glu	Tyr	Ser	Arg	Ile		
	130					135					140						
Val	Pro	Leu	Glu	Asn	Gly	Glu	Ile	Val	Val	Ser	Leu	Val	Asn	Gly	Arg		
145					150					155					160		
Pro	Gly	Ala	Leu	Asn	Phe	Ser	Tyr	Ser	Pro	Leu	Leu	Arg	Asp	Phe	Thr		
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Lys	Ala	Thr	Asn	Ile	Arg	Leu	Arg	Phe	Leu	Arg	Thr	Asn	Thr	Leu	Leu		
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Gly	His	Leu	Met	Gly	Lys	Ala	Leu	Arg	Asp	Pro	Thr	Val	Thr	Arg	Arg		
		195					200					205					
Tyr	Tyr	Tyr	Ser	Ile	Lys	Asp	Ile	Ser	Ile	Gly	Gly	Arg	Cys	Val	Cys		
	210					215					220						
His	Gly	His	Ala	Asp	Val	Cys	Asp	Ala	Lys	Asp	Pro	Leu	Asp	Pro	Phe		
225					230					235					240		
Arg	Leu	Gln	Cys	Ala	Cys	Gln	His	Asn	Thr	Cys	Gly	Gly	Ser	Cys	Asp		
				245					250					255			
Arg	Cys	Cys	Pro	Gly	Phe	Asn	Gln	Gln	Pro	Trp	Lys	Pro	Ala	Thr	Thr		
			260					265					270				
Asp	Ser	Ala	Asn	Glu	Cys	Gln	Ser	Cys	Asn	Cys	His	Gly	His	Ala	Tyr		
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Asp	Cys	Tyr	Tyr	Asp	Pro	Glu	Val	Asp	Arg	Arg	Asn	Ala	Ser	Gln	Asn		
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Gln	Asp	Asn	Val	Tyr	Gln	Gly	Gly	Gly	Val	Cys	Leu	Asp	Cys	Gln	His		
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His	Thr	Thr	Gly	Ile	Asn	Cys	Glu	Arg	Cys	Leu	Pro	Gly	Phe	Phe	Arg		
			325						330					335			
Ala	Pro	Asp	Gln	Pro	Leu	Asp	Ser	Pro	His	Val	Cys	Arg	Pro	Cys	Asp		
			340					345					350				
Cys	Glu	Ser	Asp	Phe	Thr	Asp	Gly	Thr	Cys	Glu	Asp	Leu	Thr	Gly	Arg		
		355					360					365					
Cys	Tyr	Cys	Arg	Pro	Asn	Phe	Thr	Gly	Glu	Leu	Cys	Ala	Ala	Cys	Ala		
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His	Asn	Asp	Thr	Arg	Glu	Gln	Val	Leu	Pro	Ala	Gly	Gln	Ile	Val	Asn		
				405					410					415			

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 Pro Arg Leu Gly Arg Cys Val Cys Lys Pro Asn Phe Arg Gly Ala His
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 Gln Cys Ser Ser Pro Gly Val Ala Asn Ser Leu Cys Asp Pro Glu Ser
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 Pro Tyr Cys Glu Ala Gly Ser Cys His Pro Ala Gly Leu Ala Pro Ala
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 Asn Pro Ala Leu Pro Glu Thr Gln Ala Pro Cys Met Cys Arg Ala His
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 Val Glu Gly Pro Ser Cys Asp Arg Cys Lys Pro Gly Tyr Trp Gly Leu
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 Ser Ala Ser Asn Pro Glu Gly Cys Thr Arg Cys Ser Cys Asp Pro Arg
 690 695 700
 Gly Thr Leu Gly Gly Val Thr Glu Cys Gln Gly Asn Gly Gln Cys Phe
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 Cys Lys Ala His Val Cys Gly Lys Thr Cys Ala Ala Cys Lys Asp Gly
 725 730 735

Phe Phe Gly Leu Asp Tyr Ala Asp Tyr Phe Gly Cys Arg Ser Cys Arg
740 745 750

Cys Asp Val Gly Gly Ala Leu Gly Gln Gly Cys Glu Pro Lys Thr Gly
755 760 765

Ala Cys Arg Cys Arg Pro Asn Thr Gln Gly Pro Thr Cys Ser Glu Pro
770 775 780

Ala Lys Asp His Tyr Leu Pro Asp Leu His His Met Arg Leu Glu Leu
785 790 795 800

Glu Glu Ala Ala Thr Pro Glu Gly His Ala Val Arg Phe Gly Phe Asn
805 810 815

Pro Leu Glu Phe Glu Asn Phe Ser Trp Arg Gly Tyr Ala His Met Met
820 825 830

Ala Ile Gln Pro Arg Ile Val Ala Arg Leu Asn Val Thr Ser Pro Asp
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Leu Phe Arg Leu Val Phe Arg Tyr Val Asn Arg Gly Ser Thr Ser Val
850 855 860

Asn Gly Gln Ile Ser Val Arg Glu Glu Gly Lys Leu Ser Ser Cys Thr
865 870 875 880

Asn Cys Thr Glu Gln Ser Gln Pro Val Ala Phe Pro Pro Ser Thr Glu
885 890 895

Pro Ala Phe Val Thr Val Pro Gln Arg Gly Phe Gly Glu Pro Phe Val
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Leu Asn Pro Gly Ile Trp Ala Leu Leu Val Glu Ala Glu Gly Val Leu
915 920 925

Leu Asp Tyr Val Val Leu Leu Pro Ser Thr Tyr Tyr Glu Ala Ala Leu
930 935 940

Leu Gln His Arg Val Thr Glu Ala Cys Thr Tyr Arg Pro Ser Ala Leu
945 950 955 960

His Ser Thr Glu Asn Cys Leu Val Tyr Ala His Leu Pro Leu Asp Gly
965 970 975

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

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Cys Arg Ser Pro Ala Arg Asp Thr Gln His His Leu Ala Ile Phe His 1075	1080	1085
Leu Asp Ser Glu Ala Ser Ile Arg Leu Thr Ala Glu Gln Ala His Phe 1090	1095	1100
Phe Leu His Ser Val Thr Leu Val Pro Val Glu Glu Phe Ser Thr Glu 1105	1110	1115
Phe Val Glu Pro Arg Val Phe Cys Val Ser Ser His Gly Thr Phe Asn 1125	1130	1135
Pro Ser Ser Ala Ala Cys Leu Ala Ser Arg Phe Pro Lys Pro Pro Gln 1140	1145	1150
Pro Ile Ile Leu Lys Asp Cys Gln Val Leu Pro Leu Pro Pro Asp Leu 1155	1160	1165
Pro Leu Thr Gln Ser Gln Glu Leu Ser Pro Gly Ala Pro Pro Glu Gly 1170	1175	1180
Pro Gln Pro Arg Pro Pro Thr Ala Val Asp Pro Asn Ala Glu Pro Thr 1185	1190	1195
Leu Leu Arg His Pro Gln Gly Thr Val Val Phe Thr Thr Gln Val Pro 1205	1210	1215
Thr Leu Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro Val His 1220	1225	1230
Pro Ser Phe Pro Val Glu Val Leu Ile Asn Gly Gly Arg Ile Trp Gln 1235	1240	1245
Gly His Ala Asn Ala Ser Phe Cys Pro His Gly Tyr Gly Cys Arg Thr 1250	1255	1260
Leu Val Leu Cys Glu Gly Gln Thr Met Leu Asp Val Thr Asp Asn Glu 1265	1270	1275
Leu Thr Val Thr Val Arg Val Pro Glu Gly Arg Trp Leu Trp Leu Asp 1285	1290	1295
Tyr Val Leu Ile Val Pro Glu Asp Ala Tyr Ser Ser Ser Tyr Leu Gln 1300	1305	1310
Glu Glu Pro Leu Asp Lys Ser Tyr Asp Phe Ile Ser His Cys Ala Thr 1315	1320	1325
Gln Gly Tyr His Ile Ser Pro Ser Ser Ser Ser Pro Phe Cys Arg Asn 1330	1335	1340
Ala Ala Thr Ser Leu Ser Leu Phe Tyr Asn Asn Gly Ala Leu Pro Cys 1345	1350	1355
Gly Cys His Glu Val Gly Ala Val Ser Pro Thr Cys Glu Pro Phe Gly 1365	1370	1375
Gly Gln Cys Pro Cys Arg Gly His Val Ile Gly Arg Asp Cys Ser Arg 1380	1385	1390

Cys Ala Thr Gly Tyr Trp Gly Phe Pro Asn Cys Arg Pro Cys Asp Cys
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Arg Thr Val Pro Pro Asp Cys Leu Val Cys Gln Pro Gln Ser Phe Gly
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Cys His Pro Leu Val Gly Cys Glu Glu Cys Asn Cys Ser Gly Pro Gly
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Phe Ser Leu Asp Ala Ala Asn Pro Lys Gly Cys Thr Arg Cys Phe Cys
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Phe Gly Ala Thr Glu Arg Cys Gly Asn Ser Asn Leu Ala Arg His Glu
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Phe Val Asp Met Glu Gly Trp Val Leu Leu Ser Ser Asp Arg Gln Val
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Val Pro His Glu His Arg Pro Glu Ile Glu Leu Leu His Ala Asp Leu
 1585 1590 1595 1600

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Glu Leu His Ser Glu Thr Gln Arg Gly Asp Ile Phe Ile Pro Tyr Glu
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 1955 1960 1965

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 1970 1975 1980

Gly Cys Arg Pro Cys Ala Cys Gly Pro Ala Ala Lys Gly Ser Glu Cys
 1985 1990 1995 2000

His Pro Gln Ser Gly Gln Cys His Cys Gln Pro Gly Thr Thr Gly Pro
 2005 2010 2015

Gln Cys Leu Glu Cys Ala Pro Gly Tyr Trp Gly Leu Pro Glu Lys Gly
 2020 2025 2030

Cys Arg Arg Cys Gln Cys Pro Arg Gly His Cys Asp Pro His Thr Gly

2035					2040					2045				
His Cys Thr Cys Pro	Pro Gly Leu Ser Gly	Glu Arg Cys Asp Thr Cys	2050	2055	2060									
Ser Gln Gln His Gln Val	Pro Val Pro Gly Lys Pro	Gly Gly His Gly	2065	2070	2075	2080								
Ile His Cys Glu Val Cys Asp	His Cys Val Val Leu Leu Leu	Asp Asp	2085	2090	2095									
Leu Glu Arg Ala Gly Ala Leu Leu	Pro Ala Ile Arg Glu Gln Leu Gln		2100	2105	2110									
Gly Ile Asn Ala Ser Ser Ala Ala	Trp Ala Arg Leu His Arg Leu Asn		2115	2120	2125									
Ala Ser Ile Ala Asp Leu Gln Ser Lys Leu Arg Arg	Pro Pro Gly Pro		2130	2135	2140									
Arg Tyr Gln Ala Ala Gln Gln Leu Gln Thr Leu Glu Gln Gln Ser Ile			2145	2150	2155	2160								
Ser Leu Gln Gln Asp Thr Glu Arg Leu Gly Ser Gln Ala Thr Gly Val			2165	2170	2175									
Gln Gly Gln Ala Gly Gln Leu Leu Asp Thr Thr Glu Ser Thr Leu Gly			2180	2185	2190									
Arg Ala Gln Lys Leu Leu Glu Ser Val Arg Ala Val Gly Arg Ala Leu			2195	2200	2205									
Asn Glu Leu Ala Ser Arg Met Gly Gln Gly Ser Pro Gly Asp Ala Leu			2210	2215	2220									
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Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr
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Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn
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Ser Gln Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile
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His	Thr	Leu	Gly	Asp	Asn	Leu	Leu	Asp	Ser	Arg	Met	Glu	Ile	Arg	Glu		
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Glu	Val	Glu	Gly	Met	Val	His	Gly	His	Cys	Met	Cys	Arg	His	Asn	Thr		
	290					295					300						
aag	ggc	tta	aac	tgt	gaa	ctc	tgc	atg	gat	ttc	tac	cat	gat	tta	cct	1077	
Lys	Gly	Leu	Asn	Cys	Glu	Leu	Cys	Met	Asp	Phe	Tyr	His	Asp	Leu	Pro		
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tgg	aga	cct	gct	gaa	ggc	cga	aac	agc	aac	gcc	tgt	aaa	aaa	tgt	aac	1125	
Trp	Arg	Pro	Ala	Glu	Gly	Arg	Asn	Ser	Asn	Ala	Cys	Lys	Lys	Cys	Asn		
			325						330					335			
tgc	aat	gaa	cat	tcc	atc	tct	tgt	cac	ttt	gac	atg	gct	ggt	tac	ctg	1173	
Cys	Asn	Glu	His	Ser	Ile	Ser	Cys	His	Phe	Asp	Met	Ala	Val	Tyr	Leu		
			340					345					350				
gcc	acg	ggg	aac	gtc	agc	gga	ggc	gtg	tgt	gat	gac	tgt	cag	cac	aac	1221	
Ala	Thr	Gly	Asn	Val	Ser	Gly	Gly	Val	Cys	Asp	Asp	Cys	Gln	His	Asn		
		355					360					365					
acc	atg	ggg	cgc	aac	tgt	gag	cag	tgc	aag	ccg	ttt	tac	tac	cag	cac	1269	
Thr	Met	Gly	Arg	Asn	Cys	Glu	Gln	Cys	Lys	Pro	Phe	Tyr	Tyr	Gln	His		
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cca	gag	agg	gac	atc	cga	gat	cct	aat	ttc	tgt	gaa	cga	tgt	acg	tgt	1317	
Pro	Glu	Arg	Asp	Ile	Arg	Asp	Pro	Asn	Phe	Cys	Glu	Arg	Cys	Thr	Cys		
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gac	cca	gct	ggc	tct	caa	aat	gag	gga	att	tgt	gac	agc	tat	act	gat	1365	
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	Ser Glu Asp Pro Phe Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly																			
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	Thr Ile Pro Gly Gly Asn Pro Cys Asp Ser Glu Thr Gly His Cys Tyr																			
	465		470		475															480
	tgc aag cgt ctg gtg aca gga cag cat tgt gac cag tgc ctg cca gag																			1605
	Cys Lys Arg Leu Val Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu																			
	485		490		495															
	cac tgg ggc tta agc aat gat ttg gat gga tgt cga cca tgt gac tgt																			1653
	His Trp Gly Leu Ser Asn Asp Leu Asp Gly Cys Arg Pro Cys Asp Cys																			
	500		505		510															
	gac ctt ggg gga gcc tta aac aac agt tgc ttt gcg gag tca ggc cag																			1701
	Asp Leu Gly Gly Ala Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln																			
	515		520		525															
	tgc tca tgc cgg cct cac atg att gga cgt cag tgc aac gaa gtg gaa																			1749
	Cys Ser Cys Arg Pro His Met Ile Gly Arg Gln Cys Asn Glu Val Glu																			
	530		535		540															
	cct ggt tac tac ttt gcc acc ctg gat cac tac ctc tat gaa gcg gag																			1797
	Pro Gly Tyr Tyr Phe Ala Thr Leu Asp His Tyr Leu Tyr Glu Ala Glu																			
	545		550		555															560
	gaa gcc aac ttg ggg cct ggg gtt agc ata gtg gag cgg caa tat atc																			1845
	Glu Ala Asn Leu Gly Pro Gly Val Ser Ile Val Glu Arg Gln Tyr Ile																			
	565		570		575															
	cag gac cgg att ccc tcc tgg act gga gcc ggc ttc gtc cga gtg cct																			1893
	Gln Asp Arg Ile Pro Ser Trp Thr Gly Ala Gly Phe Val Arg Val Pro																			
	580		585		590															
	gaa ggg gct tat ttg gag ttt ttc att gac aac ata cca tat tcc atg																			1941
	Glu Gly Ala Tyr Leu Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met																			
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	gag tac gac atc cta att cgc tac gag cca cag cta ccc gac cac tgg																			1989
	Glu Tyr Asp Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro Asp His Trp																			
	610		615		620															
	gaa aaa gct gtc atc aca gtg cag cga cct gga agg att cca acc agc																			2037
	Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Arg Ile Pro Thr Ser																			
	625		630		635															640
	agc cga tgt ggt aat acc atc ccc gat gat gac aac cag gtg gtg tca																			2085
	Ser Arg Cys Gly Asn Thr Ile Pro Asp Asp Asp Asn Gln Val Val Ser																			
	645		650		655															
	tta tca cca ggc tca aga tat gtc gtc ctt cct cgg ccg gtg tgc ttt																			2133
	Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe																			
	660		665		670															

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Glu Lys Gly Thr Asn Tyr Thr Val Arg Leu Glu Leu Pro Gln Tyr Thr	
675 680 685	
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Ser Ser Asp Ser Asp Val Glu Ser Pro Tyr Thr Leu Ile Asp Ser Leu	
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ggt ctc atg cca tac tgt aaa tca ctg gac atc ttc acc gtg gga ggt	2277
Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly	
705 710 715 720	
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Ser Gly Asp Gly Val Val Thr Asn Ser Ala Trp Glu Thr Phe Gln Arg	
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Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr Pro Met Thr	
740 745 750	
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Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu Leu His Gln	
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Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val	
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Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn Val Val Gly	
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aga acc tgc aac aga tgt gca cct gga act ttt ggc ttt ggc ccc agt	2565
Arg Thr Cys Asn Arg Cys Ala Pro Gly Thr Phe Gly Phe Gly Pro Ser	
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Gly Cys Lys Pro Cys Glu Cys His Leu Gln Gly Ser Val Asn Ala Phe	
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Cys Asn Pro Val Thr Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala	
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Arg Gln Cys Asp Arg Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys	
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Gln Pro Cys Gln Cys Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr	
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ggg gag tgc ttg aac tgc cag gac tac acc atg ggt cat aac tgt gaa	2805
Gly Glu Cys Leu Asn Cys Gln Asp Tyr Thr Met Gly His Asn Cys Glu	
885 890 895	
agg tgc ttg gct ggt tac tat ggc gac ccc atc att ggg tca ggt gat	2853
Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp	
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965 970 975

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980 985 990

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1010 1015 1020

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Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys
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Trp Gln Leu Ala Ser Gly Thr Gly Cys Asp Pro Cys Asn Cys Asn Ala
1075 1080 1085

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Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly	
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Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala	
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	1285 1290 1295
aac act gtg aaa gaa ctt gct gaa caa ctg gaa ttt atc aaa aac tca	4053
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Leu Leu Asp Glu Leu Ala Gly Lys Leu Gln Ser Leu Asp Leu Ser Ala	
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Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Asn Ala			
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Trp Gln Lys Ala Met Asp Leu Asp Gln Asp Val Leu Ser Ala Leu Ala			
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Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu Arg Ala			
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Asp Glu Ala Lys Gln Ser Ala Glu Asp Ile Leu Leu Lys Thr Asn Ala			
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Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn Leu Ile			
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Asp Glu Asp Ile Gln Gly Thr Gln Asn Leu Leu Thr Ser Ile Glu Ser			
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Ala His Ser Phe Gly Pro Ser Cys Asn Glu Phe Thr Gly Gln Cys Gln					
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Cys Met Pro Gly Phe Gly Gly Arg Thr Cys Ser Glu Cys Gln Glu Leu					
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Phe Trp Gly Asp Pro Asp Val Glu Cys Arg Ala Cys Asp Cys Asp Pro					
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Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala					
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 Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln Lys Leu Ser Val Thr
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 Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr Cys Ile Val Ser His
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 Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn Ser Gln Asp Pro Tyr
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 Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu Ala Glu Phe His Phe
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 Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu
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Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile Gln Asn Leu Leu Lys	
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Gln	Asn	Glu	Gly	Ile	Cys	Asp	Ser	Tyr	Thr	Asp	Phe	Ser	Thr	Gly	Leu	
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Ile	Ala	Gly	Gln	Cys	Arg	Cys	Lys	Leu	Asn	Val	Glu	Gly	Glu	His	Cys	
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Gly	Cys	Lys	Ser	Cys	Ala	Cys	Asn	Pro	Leu	Gly	Thr	Ile	Pro	Gly	Gly	
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Asn	Pro	Cys	Asp	Ser	Glu	Thr	Gly	His	Cys	Tyr	Cys	Lys	Arg	Leu	Val	
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Asn	Asp	Leu	Asp	Gly	Cys	Arg	Pro	Cys	Asp	Cys	Asp	Leu	Gly	Gly	Ala	
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Leu	Asn	Asn	Ser	Cys	Phe	Ala	Glu	Ser	Gly	Gln	Cys	Ser	Cys	Arg	Pro	
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His	Met	Ile	Gly	Arg	Gln	Cys	Asn	Glu	Val	Glu	Pro	Gly	Tyr	Tyr	Phe	
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Pro	Gly	Val	Ser	Ile	Val	Glu	Arg	Gln	Tyr	Ile	Gln	Asp	Arg	Ile	Pro	
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Ser	Trp	Thr	Gly	Ala	Gly	Phe	Val	Arg	Val	Pro	Glu	Gly	Ala	Tyr	Leu	
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Phe Leu Thr Gln Asp Ser Ala Asp Leu Asp Ser Ile Glu Ala Val Ala	
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aac ttg aca gaa gat ata cgt gaa cga gtt gaa agc ctt tct caa gta	4608
Asn Leu Thr Glu Asp Ile Arg Glu Arg Val Glu Ser Leu Ser Gln Val	
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Glu Val Ile Leu Gln His Ser Ala Ala Asp Ile Ala Arg Ala Glu Met	
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Leu Leu Glu Glu Ala Lys Arg Ala Ser Lys Ser Ala Thr Asp Val Lys	
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gtc act gca gat atg gta aag gaa gct ctg gaa gaa gca gaa aag gcc	4752
Val Thr Ala Asp Met Val Lys Glu Ala Leu Glu Glu Ala Glu Lys Ala	
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cag gtc gca gca gag aag gca att aaa caa gca gat gaa gac att caa	4800
Gln Val Ala Ala Glu Lys Ala Ile Lys Gln Ala Asp Glu Asp Ile Gln	

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Gly Thr Gln Asn Leu Leu Thr Ser Ile Glu Ser Glu Thr Ala Ala Ser				
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Asn Val Glu Glu Leu Lys Arg Lys Ala Ala Gln Asn Ser Gly Glu Ala				
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Glu Tyr Ile Glu Lys Val Val Tyr Thr Val Lys Gln Ser Ala Glu Asp				
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Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu Lys Tyr Lys Lys Val				
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Lys Ala Glu Met Leu Gln Asn Glu Ala Lys Thr Leu Leu Ala Gln Ala				
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Tyr Ser Thr Cys Leu				
	1765			
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His	Glu	Thr	Leu	Asn	Pro	Asp	Ser	His	Leu	Ile	Glu	Asn	Val	Val	Thr				
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Thr	Phe	Ala	Pro	Asn	Arg	Leu	Lys	Ile	Trp	Trp	Gln	Ser	Glu	Asn	Gly				
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Thr	His	Leu	Ile	Met	Thr	Phe	Lys	Thr	Phe	Arg	Pro	Ala	Ala	Met	Leu				
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Phe	Ala	Tyr	Asp	Cys	Glu	Ala	Ser	Phe	Pro	Gly	Ile	Ser	Thr	Gly	Pro				
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Glu	Pro	Ser	Thr	Glu	Gly	Glu	Val	Ile	Phe	Arg	Ala	Leu	Asp	Pro	Ala				
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Ser	Glu	Cys	Ala	Pro	Val	Asp	Gly	Phe	Asn	Glu	Glu	Val	Glu	Gly	Met				
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Arg Asp Pro Asn Phe Cys Glu Arg Cys Thr Cys Asp Pro Ala Gly Ser
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Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu His Trp Gly Leu Ser
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Ser Trp Thr Gly Ala Gly Phe Val Arg Val Pro Glu Gly Ala Tyr Leu
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Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe Glu Lys Gly Thr Asn
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Val Glu Ser Pro Tyr Thr Leu Ile Asp Ser Leu Val Leu Met Pro Tyr
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Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly Ser Gly Asp Gly Val
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Glu Cys His Leu Gln Gly Ser Val Asn Ala Phe Cys Asn Pro Val Thr
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Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala Arg Gln Cys Asp Arg
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Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys Gln Pro Cys Gln Cys
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Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr Gly Glu Cys Leu Asn
 850 855 860

Cys Gln Asp Tyr Thr Met Gly His Asn Cys Glu Arg Cys Leu Ala Gly
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Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp His Cys Arg Pro Cys
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Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln Phe Ala Arg Ser Cys
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Gln Cys Asp Lys Ala Thr Gly Gln Cys Leu Cys Leu Pro Asn Val Ile 1025	1030	1035
Gly Gln Asn Cys Asp Arg Cys Ala Pro Asn Thr Trp Gln Leu Ala Ser 1045	1050	1055
Gly Thr Gly Cys Asp Pro Cys Asn Cys Asn Ala Ala His Ser Phe Gly 1060	1065	1070
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Gly Gly Arg Thr Cys Ser Glu Cys Gln Glu Leu Phe Trp Gly Asp Pro 1090	1095	1100
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Glu Gly Pro Arg Cys Asp Lys Cys Thr Arg Gly Tyr Ser Gly Val Phe 1140	1145	1150
Pro Asp Cys Thr Pro Cys His Gln Cys Phe Ala Leu Trp Asp Val Ile 1155	1160	1165
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Ser Arg Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile	
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Gln Asp Arg Ile Pro Ser Trp Thr Gly Pro Gly Phe Val Arg Val Pro							
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Glu Gly Ala Tyr Leu Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met							
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Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe							
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Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly							
		705		710		715	
tca ggc gat ggg gag gtc acc aat agt gcc tgg gaa acc ttc cag cgc							2385
Ser Gly Asp Gly Glu Val Thr Asn Ser Ala Trp Glu Thr Phe Gln Arg							
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tac agg tgt ctg gag aac agc agg agt gtg gta aaa aca ccc atg aca							2433
Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr Pro Met Thr							
		740		745		750	
gat gtc tgc aga aac att atc ttc agc att tct gcc ttg att cac cag							2481
Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu Ile His Gln							
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acg ggc ctt gct tgt gaa tgt gac ccc cag gga tct ctg agt tct gtg							2529
Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val							
		770		775		780	
tgt gac ccc aat ggt ggc cag tgc cag tgc cgt cct aat gtg gtt gga							2577
Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn Val Val Gly							
		785		790		795	
						800	

aga acc tgc aac agg tgt gcc ccg ggc acc ttt ggc ttt ggc ccc aac	2625
Arg Thr Cys Asn Arg Cys Ala Pro Gly Thr Phe Gly Phe Gly Pro Asn	
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gga tgc aaa cct tgt gac tgc cat ctg caa ggg tct gcc agt gcc ttc	2673
Gly Cys Lys Pro Cys Asp Cys His Leu Gln Gly Ser Ala Ser Ala Phe	
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tgc gat gcg atc act ggc cag tgc cac tgt ttc cag ggc atc tat gct	2721
Cys Asp Ala Ile Thr Gly Gln Cys His Cys Phe Gln Gly Ile Tyr Ala	
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cgg cag tgt gac cga tgt ctc cct ggg tat tgg ggc ttt ccc agc tgc	2769
Arg Gln Cys Asp Arg Cys Leu Pro Gly Tyr Trp Gly Phe Pro Ser Cys	
850 855 860	
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Gln Pro Cys Gln Cys Asn Gly His Ala Leu Asp Cys Asp Thr Val Thr	
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Gly Glu Cys Leu Ser Cys Gln Asp Tyr Thr Thr Gly His Asn Cys Glu	
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Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp	
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His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln	
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Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys	
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Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser	
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Gly Phe Phe Gly Asn Pro Ser Asp Phe Gly Gly Ser Cys Gln Pro Cys	
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cag tgc cac cac aac att gac act acc gat cca gaa gcc tgt gac aag	3153
Gln Cys His His Asn Ile Asp Thr Thr Asp Pro Glu Ala Cys Asp Lys	
980 985 990	
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Asp Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu Gly Asp His	
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Cys Gln Leu Cys Gln Tyr Gly Tyr Tyr Gly Asp Ala Leu Arg Gln Asp	
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Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Lys Glu His Cys	
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aat ggc tct gac tgc cac tgt gac aaa gcc act ggt cag tgc tcg tgc 3345
 Asn Gly Ser Asp Cys His Cys Asp Lys Ala Thr Gly Gln Cys Ser Cys
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cga gag acc gtg gac tct gta gag aag aaa gtc aat gag ata aaa gac 3873
 Arg Glu Thr Val Asp Ser Val Glu Lys Lys Val Asn Glu Ile Lys Asp
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 Ile Leu Ala Gln Ser Pro Ala Ala Glu Pro Leu Lys Asn Ile Gly Ile
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 Leu Phe Glu Glu Ala Glu Lys Leu Thr Lys Asp Val Thr Glu Lys Met
 1250 1255 1260

gcg cag gta gaa gtg aaa tta act gat aca gct tca cag agt aac agc 4017
 Ala Gln Val Glu Val Lys Leu Thr Asp Thr Ala Ser Gln Ser Asn Ser
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aca gct gga gag ctc ggc gca ctg cag gca gaa gca gag agc ctt gac 4065

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Lys	Thr	Val	Lys	Glu	Leu	Ala	Glu	Gln	Leu	Glu	Phe	Ile	Lys	Asn	Ser	
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gat	att	cag	ggc	gcc	ttg	gat	agc	atc	acc	aag	tat	ttc	cag	atg	tct	4161
Asp	Ile	Gln	Gly	Ala	Leu	Asp	Ser	Ile	Thr	Lys	Tyr	Phe	Gln	Met	Ser	
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ctt	gag	gca	gag	aag	cgg	gtg	aat	gcc	tcc	acc	aca	gac	ccc	aac	agc	4209
Leu	Glu	Ala	Glu	Lys	Arg	Val	Asn	Ala	Ser	Thr	Thr	Asp	Pro	Asn	Ser	
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act	gtg	gag	cag	tct	gcc	ctc	acg	cga	gac	aga	gta	gaa	gat	ctg	atg	4257
Thr	Val	Glu	Gln	Ser	Ala	Leu	Thr	Arg	Asp	Arg	Val	Glu	Asp	Leu	Met	
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Leu	Glu	Arg	Glu	Ser	Pro	Phe	Lys	Glu	Gln	Gln	Glu	Glu	Gln	Ala	Arg	
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Leu	Leu	Asp	Glu	Leu	Ala	Gly	Lys	Leu	Gln	Ser	Leu	Asp	Leu	Ser	Ala	
		1380						1385					1390			
gct	gca	cag	atg	acc	tgt	gga	aca	cct	cca	ggg	gct	gac	tgt	tct	gaa	4401
Ala	Ala	Gln	Met	Thr	Cys	Gly	Thr	Pro	Pro	Gly	Ala	Asp	Cys	Ser	Glu	
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Ser	Glu	Cys	Gly	Gly	Pro	Asn	Cys	Arg	Thr	Asp	Glu	Gly	Glu	Lys	Lys	
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Cys	Gly	Gly	Pro	Gly	Cys	Gly	Gly	Leu	Val	Thr	Val	Ala	His	Ser	Ala	
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Trp	Gln	Lys	Ala	Met	Asp	Phe	Asp	Arg	Asp	Val	Leu	Ser	Ala	Leu	Ala	
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Glu	Val	Glu	Gln	Leu	Ser	Lys	Met	Val	Ser	Glu	Ala	Lys	Val	Arg	Ala	
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Asp	Glu	Ala	Lys	Gln	Asn	Ala	Gln	Asp	Val	Leu	Leu	Lys	Thr	Asn	Ala	
		1475					1480					1485				
acc	aaa	gaa	aaa	gtg	gac	aag	agc	aac	gag	gac	ctg	cgg	aac	ctc	atc	4689
Thr	Lys	Glu	Lys	Val	Asp	Lys	Ser	Asn	Glu	Asp	Leu	Arg	Asn	Leu	Ile	
	1490					1495				1500						
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Lys	Gln	Ile	Arg	Asn	Phe	Leu	Thr	Glu	Asp	Ser	Ala	Asp	Leu	Asp	Ser	
1505					1510					1515				1520		
att	gaa	gca	ggt	gct	aat	gaa	gta	ctg	aaa	agt	gga	aat	gct	agc	acg	4785
Ile	Glu	Ala	Val	Ala	Asn	Glu	Val	Leu	Lys	Ser	Gly	Asn	Ala	Ser	Thr	

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Pro Gln Gln Leu Gln Asn Leu Thr	Glu Asp Ile Arg Glu Arg Val Glu					
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acc ctc tct caa gta gag gtt att ttg cag cag agt gca gct gac att	4881					
Thr Leu Ser Gln Val Glu Val Ile Leu Gln Gln Ser Ala Ala Asp Ile						
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gcc aga gct gag ctg ttg ctt gag gaa gct aag aga gca agc aaa agt	4929					
Ala Arg Ala Glu Leu Leu Leu Glu Glu Ala Lys Arg Ala Ser Lys Ser						
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gca aca gat gtt aaa gtc act gca gac atg gtg aag gaa gca tta gaa	4977					
Ala Thr Asp Val Lys Val Thr Ala Asp Met Val Lys Glu Ala Leu Glu						
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gaa acg gca gct tct gag gaa acc ctg acc aac gcc tcc cag cgc atc	5121					
Glu Thr Ala Ala Ser Glu Glu Thr Leu Thr Asn Ala Ser Gln Arg Ile						
	1635		1640		1645	
agc aag ctt gag agg aac gtg gaa gag ctt aag cgt aaa gct gcc cag	5169					
Ser Lys Leu Glu Arg Asn Val Glu Glu Leu Lys Arg Lys Ala Ala Gln						
	1650		1655		1660	
aac tct ggg gag gca gaa tat atc gaa aaa gta gta tat tct gta aaa	5217					
Asn Ser Gly Glu Ala Glu Tyr Ile Glu Lys Val Val Tyr Ser Val Lys						
	1665		1670		1675	1680
cag aat gca gac gat gtt aaa aag act cta gat ggc gaa ctt gat gaa	5265					
Gln Asn Ala Asp Asp Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu						
	1685		1690		1695	
aag tat aag aag gta gaa agt tta att gcc caa aaa act gaa gag tca	5313					
Lys Tyr Lys Lys Val Glu Ser Leu Ile Ala Gln Lys Thr Glu Glu Ser						
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gca gat gcc agg agg aaa gct gag ctg cta caa aat gaa gca aaa aca	5361					
Ala Asp Ala Arg Arg Lys Ala Glu Leu Leu Gln Asn Glu Ala Lys Thr						
	1715		1720		1725	
ctc ttg gct caa gct aac agc aag ctc cag ctg ttg gaa gac tta gaa	5409					
Leu Leu Ala Gln Ala Asn Ser Lys Leu Gln Leu Leu Glu Asp Leu Glu						
	1730		1735		1740	
aga aaa tat gag gac aat caa aaa tac tta gaa gat aaa gct caa gaa	5457					
Arg Lys Tyr Glu Asp Asn Gln Lys Tyr Leu Glu Asp Lys Ala Gln Glu						
	1745		1750		1755	1760
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Leu Val Arg Leu Glu Gly Glu Val Arg Ser Leu Leu Lys Asp Ile Ser						
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 Glu Lys Val Ala Val Tyr Ser Thr Cys Leu
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gttttgtata aaca 5689

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 <212> PRT
 <213> Mus musculus

<400> 10
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 Thr Arg Val Cys Ala Gln Glu Pro Glu Phe Ser Tyr Gly Cys Ala Glu
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 Gly Ser Cys Tyr Pro Ala Thr Gly Asp Leu Leu Ile Gly Arg Ala Gln
 35 40 45
 Lys Leu Ser Val Thr Ser Thr Cys Gly Leu His Lys Pro Glu Pro Tyr
 50 55 60
 Cys Ile Val Ser His Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asp
 65 70 75 80
 Ser Arg Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser His Leu Ile
 85 90 95
 Glu Asn Val Val Thr Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp
 100 105 110
 Gln Ser Glu Asn Gly Val Glu Asn Val Thr Ile Gln Leu Asp Leu Glu
 115 120 125
 Ala Glu Phe His Phe Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg
 130 135 140
 Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp
 145 150 155 160
 Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ser Ser Phe Pro Gly
 165 170 175
 Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser
 180 185 190
 Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val Ile Phe Arg
 195 200 205
 Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile
 210 215 220
 Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu

225					230					235				240
His Thr Leu Gly	Asp	Asn Leu Leu Asp	Ser Arg Met Glu Ile Arg Glu	245				250					255	
Lys Tyr Tyr Tyr	Ala Val Tyr Asp	Met Val Val Arg Gly	Asn Cys Phe	260				265					270	
Cys Tyr Gly His	Ala Ser Glu Cys	Ala Pro Val Asp Gly	Val Asn Glu	275				280					285	
Glu Val Glu Gly	Met Val His Gly	His Cys Met Cys	Arg His Asn Thr	290				295					300	
Lys Gly Leu Asn	Cys Glu Leu Cys	Met Asp Phe Tyr	His Asp Leu Pro	305				310					315	320
Trp Arg Pro Ala	Glu Gly Arg Asn	Ser Asn Ala Cys	Lys Lys Cys Asn	325				330					335	
Cys Asn Glu His	Ser Ser Ser Cys	His Phe Asp Met	Ala Val Phe Leu	340				345					350	
Ala Thr Gly Asn	Val Ser Gly Gly	Val Cys Asp Asn	Cys Gln His Asn	355				360					365	
Thr Met Gly Arg	Asn Cys Glu Gln	Cys Lys Pro Phe	Tyr Phe Gln His	370				375					380	
Pro Glu Arg Asp	Ile Arg Asp Pro	Asn Leu Cys Glu	Pro Cys Thr Cys	385				390					395	400
Asp Pro Ala Gly	Ser Glu Asn Gly	Gly Ile Cys Asp	Gly Tyr Thr Asp	405				410					415	
Phe Ser Val Gly	Leu Ile Ala Gly	Gln Cys Arg Cys	Lys Leu His Val	420				425					430	
Glu Gly Glu Arg	Cys Asp Val Cys	Lys Glu Gly Phe	Tyr Asp Leu Ser	435				440					445	
Ala Glu Asp Pro	Tyr Gly Cys Lys	Ser Cys Ala Cys	Asn Pro Leu Gly	450				455					460	
Thr Ile Pro Gly	Gly Asn Pro Cys	Asp Ser Glu Thr	Gly Tyr Cys Tyr	465				470					475	480
Cys Lys Arg Leu	Val Thr Gly Gln	Arg Cys Asp Gln	Cys Leu Pro Gln	485				490					495	
His Trp Gly Leu	Ser Asn Asp Leu	Asp Gly Cys Arg	Pro Cys Asp Cys	500				505					510	
Asp Leu Gly Gly	Ala Leu Asn Asn	Ser Cys Ser Glu	Asp Ser Gly Gln	515				520					525	
Cys Ser Cys Leu	Pro His Met Ile	Gly Arg Gln Cys	Asn Glu Val Glu	530				535					540	
Ser Gly Tyr Tyr	Phe Thr Thr Leu	Asp His Tyr Ile	Tyr Glu Ala Glu	545				550					555	560

Glu Ala Asn Leu Gly Pro Gly Val Val Val Val Glu Arg Gln Tyr Ile
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 Gln Asp Arg Ile Pro Ser Trp Thr Gly Pro Gly Phe Val Arg Val Pro
 580 585 590
 Glu Gly Ala Tyr Leu Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met
 595 600 605
 Glu Tyr Glu Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro Asp His Trp
 610 615 620
 Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Lys Ile Pro Ala Ser
 625 630 635 640
 Ser Arg Cys Gly Asn Thr Val Pro Asp Asp Asp Asn Gln Val Val Ser
 645 650 655
 Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro Val Cys Phe
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 Glu Lys Gly Met Asn Tyr Thr Val Arg Leu Glu Leu Pro Gln Tyr Thr
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 Ala Ser Gly Ser Asp Val Glu Ser Pro Tyr Thr Phe Ile Asp Ser Leu
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 Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly
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 Ser Gly Asp Gly Glu Val Thr Asn Ser Ala Trp Glu Thr Phe Gln Arg
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 Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu Ile His Gln
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 Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val
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Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp
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His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln
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Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys
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Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser
 945 950 955 960

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

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Ile Leu Ala Gln Ser Pro Ala Ala Glu Pro Leu Lys Asn Ile Gly Ile 1235	1240	1245
Leu Phe Glu Glu Ala Glu Lys Leu Thr Lys Asp Val Thr Glu Lys Met 1250	1255	1260
Ala Gln Val Glu Val Lys Leu Thr Asp Thr Ala Ser Gln Ser Asn Ser 1265	1270	1275
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Lys Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile Lys Asn Ser 1300	1305	1310
Asp Ile Gln Gly Ala Leu Asp Ser Ile Thr Lys Tyr Phe Gln Met Ser 1315	1320	1325
Leu Glu Ala Glu Lys Arg Val Asn Ala Ser Thr Thr Asp Pro Asn Ser 1330	1335	1340
Thr Val Glu Gln Ser Ala Leu Thr Arg Asp Arg Val Glu Asp Leu Met 1345	1350	1355
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Leu Leu Asp Glu Leu Ala Gly Lys Leu Gln Ser Leu Asp Leu Ser Ala 1380	1385	1390
Ala Ala Gln Met Thr Cys Gly Thr Pro Pro Gly Ala Asp Cys Ser Glu 1395	1400	1405
Ser Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu Lys Lys 1410	1415	1420
Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His Ser Ala 1425	1430	1435
Trp Gln Lys Ala Met Asp Phe Asp Arg Asp Val Leu Ser Ala Leu Ala 1445	1450	1455
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Asp Glu Ala Lys Gln Asn Ala Gln Asp Val Leu Leu Lys Thr Asn Ala 1475	1480	1485
Thr Lys Glu Lys Val Asp Lys Ser Asn Glu Asp Leu Arg Asn Leu Ile 1490	1495	1500
Lys Gln Ile Arg Asn Phe Leu Thr Glu Asp Ser Ala Asp Leu Asp Ser 1505	1510	1515
Ile Glu Ala Val Ala Asn Glu Val Leu Lys Ser Gly Asn Ala Ser Thr 1525	1530	1535

Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu Arg Val Glu
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Thr Leu Ser Gln Val Glu Val Ile Leu Gln Gln Ser Ala Ala Asp Ile
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Ala Arg Ala Glu Leu Leu Leu Glu Glu Ala Lys Arg Ala Ser Lys Ser
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Gln Asn Ala Asp Asp Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu
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Lys Tyr Lys Lys Val Glu Ser Leu Ile Ala Gln Lys Thr Glu Glu Ser
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Ile	Cys	Asp	Ser	Arg	Asp	Pro	Tyr	His	Glu	Thr	Leu	Asn	Pro	Asp	Ser	
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cat	ctc	att	gag	aac	gtg	gtc	acc	aca	ttt	gct	cca	aac	cgc	ctt	aag	144
His	Leu	Ile	Glu	Asn	Val	Val	Thr	Thr	Phe	Ala	Pro	Asn	Arg	Leu	Lys	
		35					40					45				
atc	tgg	tgg	caa	tcg	gaa	aat	ggt	gtg	gag	aac	gtg	acc	atc	caa	ctg	192
Ile	Trp	Trp	Gln	Ser	Glu	Asn	Gly	Val	Glu	Asn	Val	Thr	Ile	Gln	Leu	
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Asp	Leu	Glu	Ala	Glu	Phe	His	Phe	Thr	His	Leu	Ile	Met	Thr	Phe	Lys	
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Thr	Phe	Arg	Pro	Ala	Ala	Met	Leu	Ile	Glu	Arg	Ser	Ser	Asp	Phe	Gly	
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aag	act	tgg	ggc	gtg	tac	aga	tac	ttc	gcc	tac	gac	tgt	gag	agc	tcg	336
Lys	Thr	Trp	Gly	Val	Tyr	Arg	Tyr	Phe	Ala	Tyr	Asp	Cys	Glu	Ser	Ser	
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Phe	Pro	Gly	Ile	Ser	Thr	Gly	Pro	Met	Lys	Lys	Val	Asp	Asp	Ile	Ile	
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Cys	Asp	Ser	Arg	Tyr	Ser	Asp	Ile	Glu	Pro	Ser	Thr	Glu	Gly	Glu	Val	
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cca	agg	ata	cag	aat	cta	tta	aaa	atc	acc	aac	ttg	aga	atc	aag	ttt	528
Pro	Arg	Ile	Gln	Asn	Leu	Leu	Lys	Ile	Thr	Asn	Leu	Arg	Ile	Lys	Phe	
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Val	Lys	Leu	His	Thr	Leu	Gly	Asp	Asn	Leu	Leu	Asp	Ser	Arg	Met	Glu	
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Ile	Arg	Glu	Lys	Tyr	Tyr	Tyr	Ala	Val	Tyr	Asp	Met	Val	Val	Arg	Gly	
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Val	Asn	Glu	Glu	Val	Glu	Gly	Met	Val	His	Gly	His	Cys	Met	Cys	Arg	
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His	Asn	Thr	Lys	Gly	Leu	Asn	Cys	Glu	Leu	Cys	Met	Asp	Phe	Tyr	His	

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Gln Tyr Ile Gln Asp Arg Ile Pro Ser Trp Thr Gly Pro Gly Phe Val	
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Arg Val Pro Glu Gly Ala Tyr Leu Glu Phe Phe Ile Asp Asn Ile Pro	
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Tyr Ser Met Glu Tyr Glu Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro	
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Asp His Trp Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Lys Ile	
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cca gcc agc agc cga tgt ggt aac acc gtt ccc gat gat gac aac cag	1776
Pro Ala Ser Ser Arg Cys Gly Asn Thr Val Pro Asp Asp Asp Asn Gln	
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Val Val Ser Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro	
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Val Cys Phe Glu Lys Gly Met Asn Tyr Thr Val Arg Leu Glu Leu Pro	
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Gln Tyr Thr Ala Ser Gly Ser Asp Val Glu Ser Pro Tyr Thr Phe Ile	
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Asp Ser Leu Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr	
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Phe Gln Arg Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr	
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Pro Met Thr Asp Val Cys Arg Asn Ile Ile Phe Ser Ile Ser Ala Leu	
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Ile His Gln Thr Gly Leu Ala Cys Glu Cys Asp Pro Gln Gly Ser Leu	
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Ser Ser Val Cys Asp Pro Asn Gly Gly Gln Cys Gln Cys Arg Pro Asn	
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Val Val Gly Arg Thr Cys Asn Arg Cys Ala Pro Gly Thr Phe Gly Phe	
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Ile Tyr Ala Arg Gln Cys Asp Arg Cys Leu Pro Gly Tyr Trp Gly Phe	
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Pro Ser Cys Gln Pro Cys Gln Cys Asn Gly His Ala Leu Asp Cys Asp	
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Gly Arg Gln Phe Ala Arg Ser Cys Tyr Gln Asp Pro Val Thr Leu Gln	
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Leu Ala Cys Val Cys Asp Pro Gly Tyr Ile Gly Ser Arg Cys Asp Asp	
885 890 895	
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Cys Ala Ser Gly Phe Phe Gly Asn Pro Ser Asp Phe Gly Gly Ser Cys	
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caa ccg tgt cag tgc cac cac aac att gac act acc gat cca gaa gcc	2784
Gln Pro Cys Gln Cys His His Asn Ile Asp Thr Thr Asp Pro Glu Ala	
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Cys Asp Lys Asp Thr Gly Arg Cys Leu Lys Cys Leu Tyr His Thr Glu	
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Gly Asp His Cys Gln Leu Cys Gln Tyr Gly Tyr Tyr Gly Asp Ala Leu	
945 950 955 960	
cgg caa gac tgt aga aag tgt gtc tgc aat tac ctg ggc acg gtg aag	2928
Arg Gln Asp Cys Arg Lys Cys Val Cys Asn Tyr Leu Gly Thr Val Lys	
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gaa cat tgt aat ggc tct gac tgc cac tgt gac aaa gcc act ggt cag	2976

Glu His Cys Asn Gly Ser Asp Cys His Cys Asp Lys Ala Thr Gly Gln
 980 985 990

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 Cys Ser Cys Leu Pro Asn Val Ile Gly Gln Asn Cys Asp Arg Cys Ala
 995 1000 1005

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Ser Leu Asp Lys Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile			
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aaa aac tcc gat att cag ggc gcc ttg gat agc atc acc aag tat ttc			3792
Lys Asn Ser Asp Ile Gln Gly Ala Leu Asp Ser Ile Thr Lys Tyr Phe			
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Gln Met Ser Leu Glu Ala Glu Lys Arg Val Asn Ala Ser Thr Thr Asp			
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Pro Asn Ser Thr Val Glu Gln Ser Ala Leu Thr Arg Asp Arg Val Glu			
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Asp Leu Met Leu Glu Arg Glu Ser Pro Phe Lys Glu Gln Gln Glu Glu			
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Glu Lys Lys Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala			
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Ala Leu Ala Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys			
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 Thr Phe Arg Pro Ala Ala Met Leu Ile Glu Arg Ser Ser Asp Phe Gly
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 Pro Arg Ile Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe
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 Val Lys Leu His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu
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 Asn Cys Phe Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly
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His Asn Thr Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His
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 Tyr Thr Asp Phe Ser Val Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys
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cct	act	ggc	acc	act	ggg	aag	aga	tgt	gag	ctc	tgt	gat	gat	ggc	tac	2692	
Pro	Thr	Gly	Thr	Thr	Gly	Lys	Arg	Cys	Glu	Leu	Cys	Asp	Asp	Gly	Tyr		
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ttt	gga	gac	ccc	ctg	ggg	aga	aac	ggc	cct	gtg	aga	ctt	tgc	cgc	ctg	2740	
Phe	Gly	Asp	Pro	Leu	Gly	Arg	Asn	Gly	Pro	Val	Arg	Leu	Cys	Arg	Leu		
			815					820					825				
tgc	cag	tgc	agt	gac	aac	atc	gat	ccc	aac	gca	ggt	gga	aat	tgc	aat	2788	
Cys	Gln	Cys	Ser	Asp	Asn	Ile	Asp	Pro	Asn	Ala	Val	Gly	Asn	Cys	Asn		
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cgc	ttg	acg	gga	gaa	tgc	ctg	aag	tgc	atc	tat	aac	act	gct	ggc	ttc	2836	
Arg	Leu	Thr	Gly	Glu	Cys	Leu	Lys	Cys	Ile	Tyr	Asn	Thr	Ala	Gly	Phe		
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Tyr	Cys	Asp	Arg	Cys	Lys	Asp	Gly	Phe	Phe	Gly	Asn	Pro	Leu	Ala	Pro		
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Asn	Pro	Ala	Asp	Lys	Cys	Lys	Ala	Cys	Asn	Cys	Asn	Pro	Tyr	Gly	Thr		
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Leu	Pro	His	Val	Thr	Gly	Gln	Asp	Cys	Gly	Ala	Cys	Asp	Pro	Gly	Phe		
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tac	aat	ctg	cag	agt	ggg	caa	ggc	tgt	gag	agg	tgt	gac	tgc	cat	gcc	3076	
Tyr	Asn	Leu	Gln	Ser	Gly	Gln	Gly	Cys	Glu	Arg	Cys	Asp	Cys	His	Ala		
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ttg	ggc	tcc	acc	aat	ggg	cag	tgt	gac	atc	cgc	acc	ggc	cag	tgt	gag	3124	
Leu	Gly	Ser	Thr	Asn	Gly	Gln	Cys	Asp	Ile	Arg	Thr	Gly	Gln	Cys	Glu		
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tgc	cag	ccc	ggc	atc	act	ggg	cag	cac	tgt	gag	cgc	tgt	gag	gtc	aac	3172	
Cys	Gln	Pro	Gly	Ile	Thr	Gly	Gln	His	Cys	Glu	Arg	Cys	Glu	Val	Asn		
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cac	ttt	ggg	ttt	gga	cct	gaa	ggc	tgc	aaa	ccc	tgt	gac	tgt	cat	cct	3220	
His	Phe	Gly	Phe	Gly	Pro	Glu	Gly	Cys	Lys	Pro	Cys	Asp	Cys	His	Pro		

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Glu Gly Ser Leu Ser Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys							
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Arg Glu Gly Phe Val Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr							
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ttc tac aat cgg tct tgg cct ggc tgc cag gaa tgt cca gct tgt tac						3364	
Phe Tyr Asn Arg Ser Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr							
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cgg ctg gta aag gat aag gtt gct gat cat aga gtg aag ctc cag gaa						3412	
Arg Leu Val Lys Asp Lys Val Ala Asp His Arg Val Lys Leu Gln Glu							
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Leu Glu Ser Leu Ile Ala Asn Leu Gly Thr Gly Asp Glu Met Val Thr							
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Asp Gln Ala Phe Glu Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met							
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Asp Leu Leu Arg Glu Ala Gln Asp Val Lys Asp Val Asp Gln Asn Leu							
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Met Asp Arg Leu Gln Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser							
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cgt tta cag aat atc cgg aat acc att gaa gag act gga aac ttg gct						3652	
Arg Leu Gln Asn Ile Arg Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala							
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Glu Gln Ala Arg Ala His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile							
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gtc act cag cca gaa tct aca ggg gac cca aac aac atg act ctt ttg						3796	
Val Thr Gln Pro Glu Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu							
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Ala Glu Glu Ala Arg Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp							
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Asp Ile Val Arg Val Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala							
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Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe							
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 Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser
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cag gat ctg gaa aaa caa gct gcc cga gta cat gag gag gcc aaa agg 4036
 Gln Asp Leu Glu Lys Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg
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gcc ggt gac aaa gct gtg gag atc tat gcc agc gtg gct cag ctg agc 4084
 Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser
 1260 1265 1270 1275

cct ttg gac tct gag aca ctg gag aat gaa gca aat aac ata aag atg 4132
 Pro Leu Asp Ser Glu Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met
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ctt ctg gag aaa ggc aag act gaa cag cag acc gca gac caa ctc cta 4276
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 Asp Phe Asp Arg Arg Val Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala
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cta agg aag att cct gcc atc aac cag acc atc act gaa gcc aat gaa 4468
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 Lys Thr Arg Glu Ala Gln Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala
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ctg cag gaa gca gaa aaa gag cta aag aga aaa caa gat gac gct gac 4708
 Leu Gln Glu Ala Glu Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp
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cag gac atg atg atg gca ggg atg gct tca cag gct gct caa gaa gcc 4756
 Gln Asp Met Met Met Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala
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 Glu Met Lys Val Ser Asp Leu Asp Arg Lys Val Ser Asp Leu Glu Asn
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 Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val

Asn Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys
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 405 410 415
 Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro
 420 425 430
 Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp
 435 440 445
 Pro Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val
 450 455 460
 Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly
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 Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe
 485 490 495
 Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val
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 Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala
 515 520 525
 Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg
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 Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile
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 Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn
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 Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu
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 Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val
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 Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr
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 Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile
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 Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr
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 675 680 685
 Ser Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys
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Leu Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro
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Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu
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Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu
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Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser
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Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val
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Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr
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Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu
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Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys
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Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys
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Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr
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Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser
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Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn
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Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile
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Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly
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Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser
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Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val
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Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser
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Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp

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Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu	1075	1080	1085
Ala Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln	1090	1095	1100
Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile	1105	1110	1115
Arg Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala	1125	1130	1135
His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu	1140	1145	1150
Glu Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu	1155	1160	1165
Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg	1170	1175	1180
Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val	1185	1190	1195
Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu	1205	1210	1215
Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu	1220	1225	1230
Asn Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys	1235	1240	1245
Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala	1250	1255	1260
Val Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu	1265	1270	1275
Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu	1285	1290	1295
Glu Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu	1300	1305	1310
Asp Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly	1315	1320	1325
Lys Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala	1330	1335	1340
Ala Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu	1345	1350	1355
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Gln Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg
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Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp
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Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu
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Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met
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Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg
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Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu
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Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn
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Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys
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Cys	Met	Pro	Glu	Phe	Val	Asn	Ala	Ala	Phe	Asn	Val	Thr	Val	Val	Ala	
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Thr	Asn	Thr	Cys	Gly	Thr	Pro	Pro	Glu	Glu	Tyr	Cys	Val	Gln	Thr	Gly	
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Val	Thr	Gly	Val	Thr	Lys	Ser	Cys	His	Leu	Cys	Asp	Ala	Gly	Gln	Pro	
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Asp	Thr	Thr	Trp	Trp	Gln	Ser	Gln	Thr	Met	Leu	Ala	Gly	Val	Gln	Tyr	
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Pro	Ser	Ser	Ile	Asn	Leu	Thr	Leu	His	Leu	Gly	Lys	Ala	Phe	Asp	Ile	
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Thr	Tyr	Val	Arg	Leu	Lys	Phe	His	Thr	Ser	Arg	Pro	Glu	Ser	Phe	Ala	
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Ile	Tyr	Lys	Arg	Thr	Arg	Glu	Asp	Gly	Pro	Trp	Ile	Pro	Tyr	Gln	Tyr	
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Ile	Arg	Thr	Gly	Gly	Asp	Glu	Gln	Gln	Ala	Leu	Cys	Thr	Asp	Glu	Phe	
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Ser	Asp	Ile	Ser	Pro	Leu	Thr	Gly	Gly	Asn	Val	Ala	Phe	Ser	Thr	Leu	
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Glu	Gly	Arg	Pro	Ser	Ala	Tyr	Asn	Phe	Asp	Asn	Ser	Pro	Val	Leu	Gln	
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Glu	Trp	Val	Thr	Ala	Thr	Asp	Ile	Arg	Val	Thr	Leu	Asn	Arg	Leu	Asn	
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Tyr	Tyr	Ala	Ile	Ser	Asp	Phe	Ala	Val	Gly	Gly	Arg	Cys	Lys	Cys	Asn	

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Gly	His	Ala	Ser	Glu	Cys	Met	Lys	Asn	Glu	Phe	Asp	Lys	Leu	Val	Cys					
			260					265					270							
aat	tgc	aaa	cat	aac	aca	tat	gga	gta	gac	tgt	gaa	aag	tgt	ctt	cct	864				
Asn	Cys	Lys	His	Asn	Thr	Tyr	Gly	Val	Asp	Cys	Glu	Lys	Cys	Leu	Pro					
		275					280					285								
ttc	ttc	aat	gac	cgg	ccg	tgg	agg	agg	gca	act	gcg	gaa	agt	gcc	agt	912				
Phe	Phe	Asn	Asp	Arg	Pro	Trp	Arg	Arg	Ala	Thr	Ala	Glu	Ser	Ala	Ser					
	290					295					300									
gaa	tgc	ctg	ccc	tgt	gat	tgc	aat	ggc	cga	tcc	cag	gaa	tgc	tac	ttc	960				
Glu	Cys	Leu	Pro	Cys	Asp	Cys	Asn	Gly	Arg	Ser	Gln	Glu	Cys	Tyr	Phe					
305					310					315					320					
gac	cct	gaa	ctc	tat	cgt	tcc	act	ggc	cat	ggg	ggc	cac	tgt	acc	aac	1008				
Asp	Pro	Glu	Leu	Tyr	Arg	Ser	Thr	Gly	His	Gly	Gly	His	Cys	Thr	Asn					
				325					330						335					
tgc	cag	gat	aac	aca	gat	ggc	gcc	cac	tgt	gag	agg	tgc	cga	gag	aac	1056				
Cys	Gln	Asp	Asn	Thr	Asp	Gly	Ala	His	Cys	Glu	Arg	Cys	Arg	Glu	Asn					
			340					345					350							
ttc	ttc	cgc	ctt	ggc	aac	aat	gaa	gcc	tgc	tct	tca	tgc	cac	tgt	agt	1104				
Phe	Phe	Arg	Leu	Gly	Asn	Asn	Glu	Ala	Cys	Ser	Ser	Cys	His	Cys	Ser					
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cct	gtg	ggc	tct	cta	agc	aca	cag	tgt	gat	agt	tac	ggc	aga	tgc	agc	1152				
Pro	Val	Gly	Ser	Leu	Ser	Thr	Gln	Cys	Asp	Ser	Tyr	Gly	Arg	Cys	Ser					
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Phe	His	Ser	Leu	Thr	Glu	Ala	Gly	Cys	Arg	Pro	Cys	Ser	Cys	Asp	Pro					
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tct	ggc	agc	ata	gat	gaa	tgt	aat	ggt	gaa	aca	gga	aga	tgt	ggt	tgc	1296				
Ser	Gly	Ser	Ile	Asp	Glu	Cys	Asn	Val	Glu	Thr	Gly	Arg	Cys	Val	Cys					
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Lys	Asp	Asn	Val	Glu	Gly	Phe	Asn	Cys	Glu	Arg	Cys	Lys	Pro	Gly	Phe					
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ttt	aat	ctg	gaa	tca	tct	aat	cct	cgg	ggt	tgc	aca	ccc	tgc	ttc	tgc	1392				
Phe	Asn	Leu	Glu	Ser	Ser	Asn	Pro	Arg	Gly	Cys	Thr	Pro	Cys	Phe	Cys					
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Phe	Gly	His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	Val	Tyr					
465					470					475					480					
tct	atc	tcc	tct	acc	ttt	cag	att	gat	gag	gat	ggg	tgg	cgt	gcg	gaa	1488				
Ser	Ile	Ser	Ser	Thr	Phe	Gln	Ile	Asp	Glu	Asp	Gly	Trp	Arg	Ala	Glu					
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 Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln
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 Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala
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 Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu
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 Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu
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 Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile
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gct cag ggc aat tcc tat cca agt gag acc act gtg aag tat gtc ttc 1776
 Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val Phe
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agg ctc cat gaa gca aca gat tac cct tgg agg cct gct ctt acc cct 1824
 Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr Pro
 595 600 605

ttt gaa ttt cag aag ctc cta aac aac ttg acc tct atc aag ata cgt 1872
 Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg
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 Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu
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gca agt gct cgt cct ggg cct gga gtc cct gca act tgg gtg gag tcc 1968
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 Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro Cys
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 Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr
 690 695 700

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 Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys
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tgc agt gat ggg tac tat gga gat tca act gca ggc acc tcc tcc gat 2208
 Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser Asp
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Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val Pro	
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Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr Gly	
755 760 765	
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Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly	
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Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys	
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Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys	
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aaa gcc tgc aat tgc aat ccg tat ggg acc atg aag cag cag agc agc	2592
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Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr Gly	
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Pro	Gly	Cys	Gln	Glu	Cys	Pro	Ala	Cys	Tyr	Arg	Leu	Val	Lys	Asp	Lys	
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Val	Ala	Asp	His	Arg	Val	Lys	Leu	Gln	Glu	Leu	Glu	Ser	Leu	Ile	Ala	
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Asn	Leu	Gly	Thr	Gly	Asp	Glu	Met	Val	Thr	Asp	Gln	Ala	Phe	Glu	Asp	
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Gln	Asp	Val	Lys	Asp	Val	Asp	Gln	Asn	Leu	Met	Asp	Arg	Leu	Gln	Arg	
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Val	Glu	Asn	Thr	Glu	Arg	Leu	Ile	Glu	Ile	Ala	Ser	Arg	Glu	Leu	Glu	
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Lys	Ala	Lys	Val	Ala	Ala	Ala	Asn	Val	Ser	Val	Thr	Gln	Pro	Glu	Ser	
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Thr	Gly	Asp	Pro	Asn	Asn	Met	Thr	Leu	Leu	Ala	Glu	Glu	Ala	Arg	Lys	
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Arg	Lys	Tyr	Glu	Gln	Ala	Lys	Asn	Ile	Ser	Gln	Asp	Leu	Glu	Lys	Gln	
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Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr			
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Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu Glu			
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caa ctg att gac cag aaa tta aaa gat tat gag gac ctc aga gaa gat			3840
Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp			
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atg aga ggg aag gaa ctt gaa gtc aag aac ctt ctg gag aaa ggc aag			3888
Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly Lys			
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Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala			
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Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu Gln			
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Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val			
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Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro Ala			
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Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln			
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Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys			
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Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu			
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Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met Ala			
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Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg Lys			
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 35 40 45

Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro
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His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala
 65 70 75 80

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Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile
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Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala
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Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu
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Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu Gln
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Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn
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Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser Tyr
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Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys Asn
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Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe
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Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr
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Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln
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Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala
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Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu
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Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr Pro
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Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr
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Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys
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 725 730 735

Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val Pro

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Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly			770	775	780														
Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp Asn			785	790	795														
Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys			805	810	815														
Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys			820	825	830														
Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys			835	840	845														
Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser Ser			850	855	860														
Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr Gly			865	870	875														
Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser Gly			885	890	895														
Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn Gly			900	905	910														
Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile Thr			915	920	925														
Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly Pro			930	935	940														
Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser Leu			945	950	955														
Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly			965	970	975														
Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp			980	985	990														
Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys			995	1000	1005														
Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala			1010	1015	1020														
Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu Asp			1025	1030	1035														
Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu Ala			1045	1050	1055														
Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg			1060	1065	1070														

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Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr
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Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly Lys
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Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala
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Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu Gln
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Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val
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Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro Ala
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Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln
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Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys
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Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala Thr
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Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu
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Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg Lys
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Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu
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 cgccgcagcg gg atg acg ggc ggc ggg cgg gcc gcg ctg gcc ctg cag ccc 231
 Met Thr Gly Gly Gly Arg Ala Ala Leu Ala Leu Gln Pro
 1 5 10

cgg ggg cgg ctg tgg ccg ctg ttg gct gtg ctg gcg gct gtg gcg ggc	279
Arg Gly Arg Leu Trp Pro Leu Leu Ala Val Leu Ala Ala Val Ala Gly	
15 20 25	
tgt gtc cgg gcg gcc atg gac gag tgc gcg gat gag ggc ggg cgg ccg	327
Cys Val Arg Ala Ala Met Asp Glu Cys Ala Asp Glu Gly Gly Arg Pro	
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cag cgc tgc atg ccg gag ttt gtt aat gcc gcc ttc aat gtg acc gtg	375
Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val	
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gtg gct acc aac acg tgt ggg act ccg ccc gag gag tac tgc gtg cag	423
Val Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln	
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act ggg gtg acc gga gtc act aag tcc tgt cac ctg tgc gac gcc ggc	471
Thr Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly	
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Gln Gln His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn	
95 100 105	
cag gcc gac acc acc tgg tgg caa agc cag act atg ctg gcc ggg gtg	567
Gln Ala Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val	
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Gln Tyr Pro Asn Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe	
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Asp Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser	
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Phe Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr	
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Gln Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg	
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Gly Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp	
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Glu Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser	
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Leu Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg	
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Ser	Tyr	Tyr	Tyr	Ala	Ile	Ser	Asp	Phe	Ala	Val	Gly	Gly	Arg	Cys	Lys	
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tgt	aac	gga	cat	gcc	agc	gag	tgt	gta	aag	aac	gag	ttt	gac	aaa	ctc	1095
Cys	Asn	Gly	His	Ala	Ser	Glu	Cys	Val	Lys	Asn	Glu	Phe	Asp	Lys	Leu	
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Met	Cys	Asn	Cys	Lys	His	Asn	Thr	Tyr	Gly	Val	Asp	Cys	Glu	Lys	Cys	
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ctg	cct	ttc	ttc	aat	gac	cgg	ccg	tgg	agg	agg	gcg	act	gct	gag	agc	1191
Leu	Pro	Phe	Phe	Asn	Asp	Arg	Pro	Trp	Arg	Arg	Ala	Thr	Ala	Glu	Ser	
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gcc	agc	gag	tgc	ctt	cct	tgt	gac	tgc	aat	ggc	cga	tcc	caa	gag	tgc	1239
Ala	Ser	Glu	Cys	Leu	Pro	Cys	Asp	Cys	Asn	Gly	Arg	Ser	Gln	Glu	Cys	
	335					340					345					
tac	ttt	gat	cct	gaa	cta	tac	cgt	tcc	act	gga	cat	ggt	ggc	cac	tgt	1287
Tyr	Phe	Asp	Pro	Glu	Leu	Tyr	Arg	Ser	Thr	Gly	His	Gly	Gly	His	Cys	
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acc	aac	tgc	cgg	gat	aac	aca	gat	ggt	gcc	aag	tgc	gag	agg	tgc	cgg	1335
Thr	Asn	Cys	Arg	Asp	Asn	Thr	Asp	Gly	Ala	Lys	Cys	Glu	Arg	Cys	Arg	
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gag	aat	ttc	ttc	cgc	ctg	ggg	aac	act	gaa	gcc	tgc	tct	ccg	tgc	cac	1383
Glu	Asn	Phe	Phe	Arg	Leu	Gly	Asn	Thr	Glu	Ala	Cys	Ser	Pro	Cys	His	
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Cys	Ser	Pro	Val	Gly	Ser	Leu	Ser	Thr	Gln	Cys	Asp	Ser	Tyr	Gly	Arg	
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Cys	Ser	Cys	Lys	Pro	Gly	Val	Met	Gly	Asp	Lys	Cys	Asp	Arg	Cys	Gln	
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Pro	Gly	Phe	His	Ser	Leu	Thr	Glu	Ala	Gly	Cys	Arg	Pro	Cys	Ser	Cys	
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Asp	Pro	Ser	Gly	Ser	Thr	Asp	Glu	Cys	Asn	Val	Glu	Thr	Gly	Arg	Cys	
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Val	Cys	Lys	Asp	Asn	Val	Glu	Gly	Phe	Asn	Cys	Glu	Arg	Cys	Lys	Pro	
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gga	ttt	ttt	aat	ctg	gag	tca	tct	aat	cct	aag	ggc	tgc	aca	ccc	tgc	1671
Gly	Phe	Phe	Asn	Leu	Glu	Ser	Ser	Asn	Pro	Lys	Gly	Cys	Thr	Pro	Cys	
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ttc	tgc	ttt	ggc	cat	tct	tct	gtg	tgc	aca	aat	gct	ggt	ggc	tac	agt	1719
Phe	Cys	Phe	Gly	His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	

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agg caa tat att gcc gta atc tca gac agt tac ttt cct aga tac ttc 1863 Arg Gln Tyr Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe 545 550 555			
atc gcc cct gtg aag ttc ctg ggc aac cag gtc ctg agt tat ggg cag 1911 Ile Ala Pro Val Lys Phe Leu Gly Asn Gln Val Leu Ser Tyr Gly Gln 560 565 570			
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acc ttg caa agt gct cgc cct ggg ccc gga gtc cct gca acg tgg gtg 2247 Thr Leu Gln Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val 670 675 680 685			
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tgc ctc cca ggg tac aga aga gaa act cca agc ctt gga cct tat agc 2343 Cys Leu Pro Gly Tyr Arg Arg Glu Thr Pro Ser Leu Gly Pro Tyr Ser 705 710 715			
ccg tgt gtg ctc tgt acc tgt aat ggg cac agt gag acc tgt gac ccg 2391 Pro Cys Val Leu Cys Thr Cys Asn Gly His Ser Glu Thr Cys Asp Pro 720 725 730			
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Val	Pro	Lys	Thr	Lys	Glu	Val	Val	Cys	Thr	His	Cys	Pro	Thr	Gly	Thr	
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Glu	Cys	Leu	Lys	Cys	Ile	Tyr	Asn	Thr	Ala	Gly	Phe	Tyr	Cys	Asp	Arg	
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Thr	Gly	Gln	His	Cys	Glu	Arg	Cys	Glu	Thr	Asn	His	Phe	Gly	Phe	Gly	
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cct	gaa	ggc	tgc	aaa	cct	tgt	gac	tgt	cac	cat	gaa	gga	tcc	ctt	tcg	3159
Pro	Glu	Gly	Cys	Lys	Pro	Cys	Asp	Cys	His	His	Glu	Gly	Ser	Leu	Ser	
	975					980					985					

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Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val	
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Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp	
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Lys Thr Ala Asn Glu Thr Ser Ala Glu Ala Tyr Asn Leu Leu Leu Arg	
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acc ctg gca gga gaa aat caa act gcg ctg gag att gaa gaa ctt aac	3879
Thr Leu Ala Gly Glu Asn Gln Thr Ala Leu Glu Ile Glu Glu Leu Asn	
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Arg Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp	
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atg aga gga aag gaa cat gaa gtg aag aac ctt cta gag aag ggg aaa	4167
Met Arg Gly Lys Glu His Glu Val Lys Asn Leu Leu Glu Lys Gly Lys	
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gct gaa cag cag acc gcc gac caa ctc cta gct cga gcc gat gct gcc	4215
Ala Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala	
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Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Ser Thr Leu Gln	
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Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val	
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Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala	
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atc aac cgg acc ata gct gaa gcc aat gag aag aca agg gag gcc cag	4407
Ile Asn Arg Thr Ile Ala Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln	
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Ala His Glu Ala Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr	
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agt acc aag gcg gac gca gaa aga acc ttc ggg gaa gtt aca gat ctg	4551
Ser Thr Lys Ala Asp Ala Glu Arg Thr Phe Gly Glu Val Thr Asp Leu	
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gat aat gag gtg aac ggt atg ctg agg cag cta gag gag gca gag aat	4599
Asp Asn Glu Val Asn Gly Met Leu Arg Gln Leu Glu Glu Ala Glu Asn	
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gag ctg aag agg aag caa gat gac gcc gac cag gac atg atg atg gcg	4647
Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met Ala	

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Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Leu Asn Ala Arg Lys				
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gcc aaa aac tct gtc agc agc ctc ctc agc cag ctg aac aac ctc ttg				4743
Ala Lys Asn Ser Val Ser Ser Leu Leu Ser Gln Leu Asn Asn Leu Leu				
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Asp Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu				
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Ile Glu Gly Ser Leu Asn Lys Ala Lys Asp Glu Met Lys Ala Ser Asp				
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Leu Asp Arg Lys Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu				
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gca gcc atc atg gac tat aac cgg gac ata gca gag atc att aag gat				4935
Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Ala Glu Ile Ile Lys Asp				
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Ile His Asn Leu Glu Asp Ile Lys Lys Thr Leu Pro Thr Gly Cys Phe				
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Asn Thr Pro Ser Ile Glu Lys Pro				
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<213> Mus musculus

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 35 40 45
 Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala Thr
 50 55 60
 Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly Val
 65 70 75 80
 Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Gln His
 85 90 95
 Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala Asp
 100 105 110
 Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr Pro
 115 120 125
 Asn Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile Thr
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 Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala Ile
 145 150 155 160
 Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr Tyr
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 Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe Ile
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 Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe Ser
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 Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu Gln Glu
 225 230 235 240
 Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn Thr
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 Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser Tyr Tyr
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 Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys Asn Gly
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 His Ala Ser Glu Cys Val Lys Asn Glu Phe Asp Lys Leu Met Cys Asn
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Val	Gly	Ser	Leu	Ser	Thr	Gln	Cys	Asp	Ser	Tyr	Gly	Arg	Cys	Ser	Cys
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His	Ser	Leu	Thr	Glu	Ala	Gly	Cys	Arg	Pro	Cys	Ser	Cys	Asp	Pro	Ser
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Gly	His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	Val	Tyr	Asp
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Val	Lys	Phe	Leu	Gly	Asn	Gln	Val	Leu	Ser	Tyr	Gly	Gln	Asn	Leu	Ser
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Leu	Val	Leu	Glu	Gly	Ala	Gly	Leu	Arg	Val	Ser	Val	Pro	Leu	Ile	Ala
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Gln	Gly	Asn	Ser	Tyr	Pro	Ser	Glu	Thr	Thr	Val	Lys	Tyr	Ile	Phe	Arg
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His Cys Glu Arg Cys Glu Thr Asn His Phe Gly Phe Gly Pro Glu Gly
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 Cys Lys Pro Cys Asp Cys His His Glu Gly Ser Leu Ser Leu Gln Cys
 980 985 990
 Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly Asn Arg
 995 1000 1005
 Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp Pro Gly
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 Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys Ala Ala
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 Glu His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala Asn Leu
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 Lys Met Ala Ala Asn Val Ser Ile Thr Gln Pro Glu Ser Thr Gly Glu
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 Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala Lys Thr Ala
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 Gly Glu Asn Gln Thr Ala Leu Glu Ile Glu Glu Leu Asn Arg Lys Tyr
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 Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val Glu Ile Tyr
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 Ala Ser Val Ala Gln Leu Thr Pro Val Asp Ser Glu Ala Leu Glu Asn
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 Glu Ala Asn Lys Ile Lys Lys Glu Ala Ala Asp Leu Asp Arg Leu Ile

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Lys	Glu His Glu Val Lys Asn Leu Leu Glu Lys Gly Lys Ala Glu Gln				
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Gln	Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu				
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Ala	Glu Glu Ala Ala Lys Lys Gly Arg Ser Thr Leu Gln Glu Ala Asn				
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Asp	Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val Asn Asp Asn				
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Lys	Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala Ile Asn Arg				
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Thr	Ile Ala Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln Leu Ala Leu				
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Gly	Asn Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys Ala His Glu				
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Ala	Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys				
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Ala	Asp Ala Glu Arg Thr Phe Gly Glu Val Thr Asp Leu Asp Asn Glu				
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Val	Asn Gly Met Leu Arg Gln Leu Glu Glu Ala Glu Asn Glu Leu Lys				
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Arg	Lys Gln Asp Asp Ala Asp Gln Asp Met Met Met Ala Gly Met Ala				
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Ser	Gln Ala Ala Gln Glu Ala Glu Leu Asn Ala Arg Lys Ala Lys Asn				
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Ser	Val Ser Ser Leu Leu Ser Gln Leu Asn Asn Leu Leu Asp Gln Leu				
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Gly	Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu Ile Glu Gly				
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Ser	Leu Asn Lys Ala Lys Asp Glu Met Lys Ala Ser Asp Leu Asp Arg				
	1540		1545		1550
Lys	Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu Ala Ala Ile				
	1555		1560		1565
Met	Asp Tyr Asn Arg Asp Ile Ala Glu Ile Ile Lys Asp Ile His Asn				
	1570		1575		1580
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 Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala Thr Asn
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 acg tgt ggg act ccg ccc gag gag tac tgc gtg cag act ggg gtg acc 144
 Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly Val Thr
 35 40 45
 gga gtc act aag tcc tgt cac ctg tgc gac gcc ggc cag cag cac ctg 192
 Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Gln His Leu
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 caa cac ggg gca gcc ttc ctg acc gac tac aac aac cag gcc gac acc 240
 Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala Asp Thr
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 acc tgg tgg caa agc cag act atg ctg gcc ggg gtg cag tac ccc aac 288
 Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr Pro Asn
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 Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala Ile Tyr
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 Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr Tyr Ser
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 acc gga ggg gac gag cag cag gcc ttg tgt act gat gaa ttc agt gac 528
 Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe Ser Asp
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 Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu Glu Gly
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Asn	Asp	Arg	Pro	Trp	Arg	Arg	Ala	Thr	Ala	Glu	Ser	Ala	Ser	Glu	Cys	
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Asn	Val	Glu	Gly	Phe	Asn	Cys	Glu	Arg	Cys	Lys	Pro	Gly	Phe	Phe	Asn	

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Leu	Glu	Ser	Ser	Asn	Pro	Lys	Gly	Cys	Thr	Pro	Cys	Phe	Cys	Phe	Gly				
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cat	tct	tct	gtg	tgc	aca	aat	gct	gtt	ggc	tac	agt	gtt	tat	gac	atc				1440
His	Ser	Ser	Val	Cys	Thr	Asn	Ala	Val	Gly	Tyr	Ser	Val	Tyr	Asp	Ile				
	465				470					475					480				
tcc	tcc	acc	ttt	cag	att	gat	gag	gat	ggg	tgg	cgc	gtg	gag	cag	aga				1488
Ser	Ser	Thr	Phe	Gln	Ile	Asp	Glu	Asp	Gly	Trp	Arg	Val	Glu	Gln	Arg				
				485					490					495					
gat	ggc	tcg	gag	gcg	tct	ctg	gag	tgg	tcc	tca	gac	agg	caa	tat	att				1536
Asp	Gly	Ser	Glu	Ala	Ser	Leu	Glu	Trp	Ser	Ser	Asp	Arg	Gln	Tyr	Ile				
			500					505					510						
gcc	gta	atc	tca	gac	agt	tac	ttt	cct	aga	tac	ttc	atc	gcc	cct	gtg				1584
Ala	Val	Ile	Ser	Asp	Ser	Tyr	Phe	Pro	Arg	Tyr	Phe	Ile	Ala	Pro	Val				
		515					520					525							
aag	ttc	ctg	ggc	aac	cag	gtc	ctg	agt	tat	ggg	cag	aat	ctt	tcc	ttc				1632
Lys	Phe	Leu	Gly	Asn	Gln	Val	Leu	Ser	Tyr	Gly	Gln	Asn	Leu	Ser	Phe				
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tcc	ttc	cga	gtg	gac	aga	cga	gac	act	cgc	ctc	tcc	gca	gag	gac	ctt				1680
Ser	Phe	Arg	Val	Asp	Arg	Arg	Asp	Thr	Arg	Leu	Ser	Ala	Glu	Asp	Leu				
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Val	Leu	Glu	Gly	Ala	Gly	Leu	Arg	Val	Ser	Val	Pro	Leu	Ile	Ala	Gln				
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ttt	cag	aag	ctc	ctg	aac	aac	ttg	acc	tct	atc	aag	atc	cgt	ggt	aca				1872
Phe	Gln	Lys	Leu	Leu	Asn	Asn	Leu	Thr	Ser	Ile	Lys	Ile	Arg	Gly	Thr				
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Tyr	Ser	Glu	Arg	Ser	Ala	Gly	Tyr	Leu	Asp	Asp	Val	Thr	Leu	Gln	Ser				
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gct	cgc	cct	ggg	ccc	gga	gtc	cct	gca	acg	tgg	gtg	gag	tcc	tgc	acc				1968
Ala	Arg	Pro	Gly	Pro	Gly	Val	Pro	Ala	Thr	Trp	Val	Glu	Ser	Cys	Thr				
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tgt	cca	gtg	gga	tac	ggg	gga	cag	ttc	tgt	gag	acg	tgc	ctc	cca	ggg				2016
Cys	Pro	Val	Gly	Tyr	Gly	Gly	Gln	Phe	Cys	Glu	Thr	Cys	Leu	Pro	Gly				
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tac	aga	aga	gaa	act	cca	agc	ctt	gga	cct	tat	agc	ccg	tgt	gtg	ctc				2064
Tyr	Arg	Arg	Glu	Thr	Pro	Ser	Leu	Gly	Pro	Tyr	Ser	Pro	Cys	Val	Leu				
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Lys Glu Val Val Cys Thr His Cys Pro Thr Gly Thr Ala Gly Lys Arg	
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Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly Ser Asn	
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785 790 795 800	
ccc aac gcg gtt ggc aac tgc aac cgc ctg acg ggc gag tgc ctg aag	2448
Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys Leu Lys	
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Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys Glu Gly	
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Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys Lys Ala	
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Cys Ala Cys Asn Tyr Gly Thr Val Gln Gln Gln Ser Ser Cys Asn Pro	
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Val Thr Gly Gln Cys Gln Cys Leu Pro His Val Ser Gly Arg Asp Cys	
865 870 875 880	
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Gly Thr Cys Asp Pro Gly Tyr Tyr Asn Leu Gln Ser Gly Gln Gly Cys	
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Lys Pro Cys Asp Cys His His Glu Gly Ser Leu Ser Leu Gln Cys Lys	
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Met Ala Ala Asn Val Ser Ile Thr Gln Pro Glu Ser Thr Gly Glu Pro	
1125 1130 1135	
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Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Arg Leu Ala Glu Arg	
1140 1145 1150	
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His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala Lys Thr Ala Asn	
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Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln Ala Ala Arg Val	
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His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala	
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Ser Val Ala Gln Leu Thr Pro Val Asp Ser Glu Ala Leu Glu Asn Glu	
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Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly Lys	
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 Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Gln His Leu
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 Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys Lys Glu Gly
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Gly Ala Ala Arg Ala Arg Glu Glu Ala Gly Gly Gly Phe Ser Leu His
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Pro Pro Tyr Phe Asn Leu Ala Glu Gly Ala Arg Ile Ala Ala Ser Ala
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Asp Leu Tyr Cys Lys Leu Val Gly Gly Pro Val Ala Gly Gly Asp Pro
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Ser Asn Lys Ala His Pro Ala Ser Asn Ala Ile Asp Gly Thr Glu Arg
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Trp Trp Gln Ser Pro Pro Leu Ser Arg Gly Leu Glu Tyr Asn Glu Val
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Asn Val Thr Leu Asp Leu Gly Gln Val Phe His Val Ala Tyr Val Leu
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Ser Met Asp Phe Gly Arg Thr Tyr Gln Pro Trp Gln Phe Phe Ala Ser
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Pro Gly Ala Met Asn Phe Ser Tyr Ser Pro Leu Leu Arg Glu Phe Thr	
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Lys Ala Thr Asn Val Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu	
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Gly His Leu Met Gly Lys Ala Leu Arg Asp Pro Thr Val Thr Arg Arg	
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Cys Tyr Cys Arg Pro Asn Phe Ser Gly Glu Arg Cys Asp Val Cys Ala	
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Gln	Cys	Arg	Cys	Arg	Val	Gly	Phe	Glu	Gly	Ala	Thr	Cys	Asp	Arg	Cys	
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Phe	Pro	Ser	Cys	Val	Pro	Cys	His	Cys	Ser	Ala	Glu	Gly	Ser	Leu	His	
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ccg ctg acc cac gcg cag gat ctc act cca gcc acg tcc cca gct gga	3853
Pro Leu Thr His Ala Gln Asp Leu Thr Pro Ala Thr Ser Pro Ala Gly	
1250 1255 1260	
ccc cga cct cgg ccc ccc acc gct gtg gac cct gat gca gag ccc acc	3901
Pro Arg Pro Arg Pro Pro Thr Ala Val Asp Pro Asp Ala Glu Pro Thr	
1265 1270 1275	
ctg ctg cgt gag ccc cag gcc acc gtg gtc ttc acc acc cat gtg ccc	3949
Leu Leu Arg Glu Pro Gln Ala Thr Val Val Phe Thr Thr His Val Pro	
1280 1285 1290	
acg ctg ggc cgc tat gcc ttc ctg ctg cac ggc tac cag cca gcc cac	3997
Thr Leu Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro Ala His	
1295 1300 1305 1310	
ccc acc ttc ccc gtg gaa gtc ctc atc aac gcc ggc cgc gtg tgg cag	4045
Pro Thr Phe Pro Val Glu Val Leu Ile Asn Ala Gly Arg Val Trp Gln	
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ggc cac gcc aac gcc agc ttc tgt cca cat ggc tac ggc tgc cgc acc	4093
Gly His Ala Asn Ala Ser Phe Cys Pro His Gly Tyr Gly Cys Arg Thr	
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ctg gtg gtg tgt gag ggc cag gcc ctg ctg gac gtg acc cac agc gag	4141
Leu Val Val Cys Glu Gly Gln Ala Leu Leu Asp Val Thr His Ser Glu	
1345 1350 1355	
ctc act gtg acc gtg cgt gtg ccc gag ggc cgg tgg ctc tgg ctg gat	4189
Leu Thr Val Thr Val Arg Val Pro Glu Gly Arg Trp Leu Trp Leu Asp	
1360 1365 1370	
tat gta ctc gtg gtc cct gag aac gtc tac agc ttt ggc tac ctc cgg	4237
Tyr Val Leu Val Val Pro Glu Asn Val Tyr Ser Phe Gly Tyr Leu Arg	
1375 1380 1385 1390	
gag gag ccc ctg gat aaa tcc tat gac ttc atc agc cac tgc gca gcc	4285
Glu Glu Pro Leu Asp Lys Ser Tyr Asp Phe Ile Ser His Cys Ala Ala	
1395 1400 1405	
cag ggc tac cac atc agc ccc agc agc tca tcc ctg ttc tgc cga aac	4333
Gln Gly Tyr His Ile Ser Pro Ser Ser Ser Ser Leu Phe Cys Arg Asn	
1410 1415 1420	
gct gct gct tcc ctc tcc ctc ttc tat aac aac gga gcc cgt cca tgt	4381
Ala Ala Ala Ser Leu Ser Leu Phe Tyr Asn Asn Gly Ala Arg Pro Cys	
1425 1430 1435	
ggc tgc cac gaa gta ggt gct aca ggc ccc acg tgt gag ccc ttc ggg	4429

Gly Cys His Glu Val Gly Ala Thr Gly Pro Thr Cys Glu Pro Phe Gly	
1440	1445 1450
ggc cag tgt ccc tgc cat gcc cat gtc att ggc cgt gac tgc tcc cgc	4477
Gly Gln Cys Pro Cys His Ala His Val Ile Gly Arg Asp Cys Ser Arg	
1455	1460 1465 1470
tgt gcc acc gga tac tgg ggc ttc ccc aac tgc agg ccc tgt gac tgc	4525
Cys Ala Thr Gly Tyr Trp Gly Phe Pro Asn Cys Arg Pro Cys Asp Cys	
	1475 1480 1485
ggt gcc cgc ctc tgt gac gag ctc acg ggc cag tgc atc tgc ccg cca	4573
Gly Ala Arg Leu Cys Asp Glu Leu Thr Gly Gln Cys Ile Cys Pro Pro	
	1490 1495 1500
cgc acc atc ccg ccc gac tgc ctg tgc cag ccc cag acc ttt ggc	4621
Arg Thr Ile Pro Pro Asp Cys Leu Leu Cys Gln Pro Gln Thr Phe Gly	
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Cys His Pro Leu Val Gly Cys Glu Glu Cys Asn Cys Ser Gly Pro Gly	
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atc cag gag ctc aca gac cct acc tgt gac aca gac agc ggc cag tgc	4717
Ile Gln Glu Leu Thr Asp Pro Thr Cys Asp Thr Asp Ser Gly Gln Cys	
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Lys Cys Arg Pro Asn Val Thr Gly Arg Arg Cys Asp Thr Cys Ser Pro	
	1555 1560 1565
ggc ttc cat ggc tac ccc cgc tgc cgc ccc tgt gac tgt cac gag gcg	4813
Gly Phe His Gly Tyr Pro Arg Cys Arg Pro Cys Asp Cys His Glu Ala	
	1570 1575 1580
ggc act gcg cct ggc gtg tgt gac ccc ctc aca ggg cag tgc tac tgt	4861
Gly Thr Ala Pro Gly Val Cys Asp Pro Leu Thr Gly Gln Cys Tyr Cys	
	1585 1590 1595
aag gag aac gtg cag ggc ccc aaa tgt gac cag tgc agc ctt ggg acc	4909
Lys Glu Asn Val Gln Gly Pro Lys Cys Asp Gln Cys Ser Leu Gly Thr	
	1600 1605 1610
ttc tca ctg gat gct gcc aac ccc aaa ggt tgc acc cgc tgc ttc tgc	4957
Phe Ser Leu Asp Ala Ala Asn Pro Lys Gly Cys Thr Arg Cys Phe Cys	
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ttt ggg gcc acg gag cgc tgc cgg agc tgc tcc tac acc cgc cag gag	5005
Phe Gly Ala Thr Glu Arg Cys Arg Ser Ser Ser Tyr Thr Arg Gln Glu	
	1635 1640 1645
ttc gtg gat atg gag gga tgg gtg ctg ctg agc act gac cgg cag gtg	5053
Phe Val Asp Met Glu Gly Trp Val Leu Leu Ser Thr Asp Arg Gln Val	
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gtg ccc cac gag egg cag cca ggg acg gag atg ctc cgt gca gac ctg	5101
Val Pro His Glu Arg Gln Pro Gly Thr Glu Met Leu Arg Ala Asp Leu	
	1665 1670 1675
cgg cac gtg cct gag gct gtg ccc gag gct ttc ccc gag ctg tac tgg	5149
Arg His Val Pro Glu Ala Val Pro Glu Ala Phe Pro Glu Leu Tyr Trp	

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cag gcc cca ccc tcc tac ctg ggg gac cgg gtg tca tcc tac ggt ggg			5197
Gln Ala Pro Pro Ser Tyr Leu Gly Asp Arg Val Ser Ser Tyr Gly Gly			
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acc ctc cgt tat gaa ctg cac tca gag acc cag cgg gga gat gtc ttt			5245
Thr Leu Arg Tyr Glu Leu His Ser Glu Thr Gln Arg Gly Asp Val Phe			
	1715	1720	1725
gtc ccc atg gag agc agg ccg gat gtg gtg ctg cag ggc aac cag atg			5293
Val Pro Met Glu Ser Arg Pro Asp Val Val Leu Gln Gly Asn Gln Met			
	1730	1735	1740
agc atc aca ttc ctg gag ccg gca tac ccc acg cct ggc cac gtt cac			5341
Ser Ile Thr Phe Leu Glu Pro Ala Tyr Pro Thr Pro Gly His Val His			
	1745	1750	1755
cgt ggg cag ctg cag ctg gtg gag ggg aac ttc cgg cat acg gag act			5389
Arg Gly Gln Leu Gln Leu Val Glu Gly Asn Phe Arg His Thr Glu Thr			
	1760	1765	1770
cgc aac act gtg tcc cgc gag gag ctc atg atg gtg ctg gcc agc ctg			5437
Arg Asn Thr Val Ser Arg Glu Glu Leu Met Met Val Leu Ala Ser Leu			
	1775	1780	1785
gag cag ctg cag atc cgt gcc ctc ttc tca cag atc tcc tcg gct gtc			5485
Glu Gln Leu Gln Ile Arg Ala Leu Phe Ser Gln Ile Ser Ser Ala Val			
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tcc ctg cgc agg gtg gca ctg gag gtg gcc agc cca gca ggc cag ggg			5533
Ser Leu Arg Arg Val Ala Leu Glu Val Ala Ser Pro Ala Gly Gln Gly			
	1810	1815	1820
gcc ctg gcc agc aat gtg gag ctg tgc ctg tgc ccc gcc agc tac cgg			5581
Ala Leu Ala Ser Asn Val Glu Leu Cys Leu Cys Pro Ala Ser Tyr Arg			
	1825	1830	1835
ggg gac tca tgc cag gaa tgt gcc ccc ggc ttc tat cgg gac gtc aaa			5629
Gly Asp Ser Cys Gln Glu Cys Ala Pro Gly Phe Tyr Arg Asp Val Lys			
	1840	1845	1850
ggt ctc ttc ctg ggc cga tgt gtc cct tgt cag tgc cat gga cac tca			5677
Gly Leu Phe Leu Gly Arg Cys Val Pro Cys Gln Cys His Gly His Ser			
	1855	1860	1865
gac cgc tgc ctc cct ggc tct ggc gtc tgt gtg gac tgc cag cac aac			5725
Asp Arg Cys Leu Pro Gly Ser Gly Val Cys Val Asp Cys Gln His Asn			
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acc gaa ggg gcc cac tgt gag cgc tgc cag gct ggc ttc atg agc agc			5773
Thr Glu Gly Ala His Cys Glu Arg Cys Gln Ala Gly Phe Met Ser Ser			
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agg gac gac ccc agc gcc ccc tgt gtc agc tgc ccc tgc ccc ctc tca			5821
Arg Asp Asp Pro Ser Ala Pro Cys Val Ser Cys Pro Cys Pro Leu Ser			
	1905	1910	1915
gtg cct tcc aac aac ttc gcc gag ggc tgt gtc ctg cga ggc ggc cgc			5869
Val Pro Ser Asn Asn Phe Ala Glu Gly Cys Val Leu Arg Gly Gly Arg			
	1920	1925	1930

acc cag tgc ctc tgc aaa cct ggt tat gca ggt gcc tcc tgc gag cgg	5917		
Thr Gln Cys Leu Cys Lys Pro Gly Tyr Ala Gly Ala Ser Cys Glu Arg			
1935	1940	1945	1950
tgt gcg ccc gga ttc ttt ggg aac cca ctg gtg ctg ggc agc tcc tgc	5965		
Cys Ala Pro Gly Phe Phe Gly Asn Pro Leu Val Leu Gly Ser Ser Cys			
	1955	1960	1965
cag cca tgc gac tgc agc ggc aac ggt gac ccc aac ttg ctc ttc agc	6013		
Gln Pro Cys Asp Cys Ser Gly Asn Gly Asp Pro Asn Leu Leu Phe Ser			
	1970	1975	1980
gac tgc gac ccc ctg acg ggc gcc tgc cgt ggc tgc ctg cgc cac acc	6061		
Asp Cys Asp Pro Leu Thr Gly Ala Cys Arg Gly Cys Leu Arg His Thr			
	1985	1990	1995
act ggg ccc cgc tgc gag atc tgt gcc ccc ggc ttc tac ggc aac gcc	6109		
Thr Gly Pro Arg Cys Glu Ile Cys Ala Pro Gly Phe Tyr Gly Asn Ala			
2000	2005	2010	
ctg ctg ccc ggc aac tgc acc cgg tgc gac tgt acc cca tgt ggg aca	6157		
Leu Leu Pro Gly Asn Cys Thr Arg Cys Asp Cys Thr Pro Cys Gly Thr			
2015	2020	2025	2030
gag gcc tgc gac ccc cac agc ggg cac tgc ctg tgc aag gcg ggc gtg	6205		
Glu Ala Cys Asp Pro His Ser Gly His Cys Leu Cys Lys Ala Gly Val			
	2035	2040	2045
act ggg cgg cgc tgt gac cgc tgc cag gag gga cat ttt ggt ttc aat	6253		
Thr Gly Arg Arg Cys Asp Arg Cys Gln Glu Gly His Phe Gly Phe Asn			
	2050	2055	2060
ggc tgc ggg ggc tgc cgc ccg tgt gct tgt gga ccg gcc gcc gag ggc	6301		
Gly Cys Gly Gly Cys Arg Pro Cys Ala Cys Gly Pro Ala Ala Glu Gly			
2065	2070	2075	
tcc gag tgc cac ccc cag agc gga cag tgc cac tgc cga cca ggg acc	6349		
Ser Glu Cys His Pro Gln Ser Gly Gln Cys His Cys Arg Pro Gly Thr			
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atg gga ccc cag tgc cgc gag tgt gcc cct ggc tac tgg ggg ctc cct	6397		
Met Gly Pro Gln Cys Arg Glu Cys Ala Pro Gly Tyr Trp Gly Leu Pro			
2095	2100	2105	2110
gag cag ggc tgc agg cgc tgc cag tgc cct ggg ggc cgc tgt gac cct	6445		
Glu Gln Gly Cys Arg Arg Cys Gln Cys Pro Gly Gly Arg Cys Asp Pro			
	2115	2120	2125
cac acg ggc cgc tgc aac tgc ccc ccg ggg ctc agc ggg gag cgc tgc	6493		
His Thr Gly Arg Cys Asn Cys Pro Pro Gly Leu Ser Gly Glu Arg Cys			
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gac acc tgc agc cag cag cat cag gtg cct gtt cca ggc ggg cct gtg	6541		
Asp Thr Cys Ser Gln Gln His Gln Val Pro Val Pro Gly Gly Pro Val			
	2145	2150	2155
ggc cac agc atc cac tgt gaa gtg tgt gac cac tgt gtg gtc ctg ctc	6589		
Gly His Ser Ile His Cys Glu Val Cys Asp His Cys Val Val Leu Leu			
2160	2165	2170	

ctg gat gac ctg gaa cgg gcc ggc gcc ctc ctc ccc gcc att cac gag 6637
 Leu Asp Asp Leu Glu Arg Ala Gly Ala Leu Leu Pro Ala Ile His Glu
 2175 2180 2185 2190

 caa ctg cgt ggc atc aat gcc agc tcc atg gcc tgg gcc cgt ctg cac 6685
 Gln Leu Arg Gly Ile Asn Ala Ser Ser Met Ala Trp Ala Arg Leu His
 2195 2200 2205

 agg ctg aac gcc tcc atc gct gac ctg cag agc cag ctc cgg agc ccc 6733
 Arg Leu Asn Ala Ser Ile Ala Asp Leu Gln Ser Gln Leu Arg Ser Pro
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 ctg ggc ccc cgc cat gag acg gca cag cag ctg gag gtg ctg gag cag 6781
 Leu Gly Pro Arg His Glu Thr Ala Gln Gln Leu Glu Val Leu Glu Gln
 2225 2230 2235

 cag agc aca agc ctc ggg cag gac gca cgg cgg cta gcc gcc cag gcc 6829
 Gln Ser Thr Ser Leu Gly Gln Asp Ala Arg Arg Leu Gly Gly Gln Ala
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 Val Gly Thr Arg Asp Gln Ala Ser Gln Leu Leu Ala Gly Thr Glu Ala
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 aca ctg ggc cat gcg aag acg ctg ttg gcg gcc atc cgg gct gtg gac 6925
 Thr Leu Gly His Ala Lys Thr Leu Leu Ala Ala Ile Arg Ala Val Asp
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 Arg Thr Leu Ser Glu Leu Met Ser Gln Thr Gly His Leu Gly Leu Ala
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 aat gcc tcg gct cca tca ggt gag cag ctg ctc cgg aca ctg gcc gag 7021
 Asn Ala Ser Ala Pro Ser Gly Glu Gln Leu Leu Arg Thr Leu Ala Glu
 2305 2310 2315

 gtg gag cgg ctg ctc tgg gag atg cgg gcc cgg gac ctg ggg gcc ccg 7069
 Val Glu Arg Leu Leu Trp Glu Met Arg Ala Arg Asp Leu Gly Ala Pro
 2320 2325 2330

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 Gln Ala Ala Ala Glu Ala Glu Leu Ala Ala Ala Gln Arg Leu Leu Ala
 2335 2340 2345 2350

 cgg gtg cag gag cag ctg agc agc ctc tgg gag gag aac cag gca ctg 7165
 Arg Val Gln Glu Gln Leu Ser Ser Leu Trp Glu Glu Asn Gln Ala Leu
 2355 2360 2365

 gcc aca caa acc cgc gac cgg ctg gcc cag cac gag gcc gcc ctc atg 7213
 Ala Thr Gln Thr Arg Asp Arg Leu Ala Gln His Glu Ala Gly Leu Met
 2370 2375 2380

 gac ctg cga gag gct ttg aac cgg gca gtg gac gcc aca cgg gag gcc 7261
 Asp Leu Arg Glu Ala Leu Asn Arg Ala Val Asp Ala Thr Arg Glu Ala
 2385 2390 2395

 cag gag ctc aac agc cgc aac cag gag cgc ctg gag gaa gcc ctg caa 7309
 Gln Glu Leu Asn Ser Arg Asn Gln Glu Arg Leu Glu Glu Ala Leu Gln
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 agg aag cag gag ctg tcc cgg gac aat gcc acc ctg cag gcc act ctg 7357

Arg Lys Gln Glu Leu Ser	Arg Asp Asn Ala Thr Leu Gln Ala Thr Leu	
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cat gcg gct agg gac acc ctg gcc agc gtc ttc aga ttg ctg cac agc		7405
His Ala Ala Arg Asp Thr Leu Ala Ser Val Phe Arg Leu Leu His Ser		
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ctg gac cag gct aag gag gag ctg gag cgc ctc gcc gcc agc ctg gac		7453
Leu Asp Gln Ala Lys Glu Glu Leu Glu Arg Leu Ala Ala Ser Leu Asp		
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ggg gct cgg acc cca ctg ctg cag agg atg cag acc ttc tcc ccg gcg		7501
Gly Ala Arg Thr Pro Leu Leu Gln Arg Met Gln Thr Phe Ser Pro Ala		
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ggc agc aag ctg cgt cta gtg gag gcc gcc gag gcc cac gca cag cag		7549
Gly Ser Lys Leu Arg Leu Val Glu Ala Ala Glu Ala His Ala Gln Gln		
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Leu Gly Gln Leu Ala Leu Asn Leu Ser Ser Ile Ile Leu Asp Val Asn		
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cag gac cgc ctc acc cag agg gcc atc gag gcc tcc aac gcc tac agc		7645
Gln Asp Arg Leu Thr Gln Arg Ala Ile Glu Ala Ser Asn Ala Tyr Ser		
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cgc atc ctg cag gcc gtg cag gct gcc gag gat gct gct ggc cag gcc		7693
Arg Ile Leu Gln Ala Val Gln Ala Ala Glu Asp Ala Ala Gly Gln Ala		
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Leu Gln Gln Ala Asp His Thr Trp Ala Thr Val Val Arg Gln Gly Leu		
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Val Asp Arg Ala Gln Gln Leu Leu Ala Asn Ser Thr Ala Leu Glu Glu		
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gcc atg ctc cag gaa cag cag agg ctg ggc ctt gtg tgg gct gcc ctc		7837
Ala Met Leu Gln Glu Gln Gln Arg Leu Gly Leu Val Trp Ala Ala Leu		
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cag ggt gcc agg acc cag ctc cga gat gtc cgg gcc aag aag gac cag		7885
Gln Gly Ala Arg Thr Gln Leu Arg Asp Val Arg Ala Lys Lys Asp Gln		
2595	2600	2605
ctg gag gcg cac atc cag gcg gcg cag gcc atg ctt gcc atg gac aca		7933
Leu Glu Ala His Ile Gln Ala Ala Gln Ala Met Leu Ala Met Asp Thr		
2610	2615	2620
gac gag aca agc aag aag atc gca cat gcc aag gct gtg gct gct gaa		7981
Asp Glu Thr Ser Lys Lys Ile Ala His Ala Lys Ala Val Ala Ala Glu		
2625	2630	2635
gcc cag gac acc gcc acc cgt gtg cag tcc cag ctg cag gcc atg cag		8029
Ala Gln Asp Thr Ala Thr Arg Val Gln Ser Gln Leu Gln Ala Met Gln		
2640	2645	2650
gag aat gtg gag cgg tgg cag ggc cag tac gag ggc ctg cgg ggc cag		8077
Glu Asn Val Glu Arg Trp Gln Gly Gln Tyr Glu Gly Leu Arg Gly Gln		

2655	2660	2665	2670	
gac ctg ggc cag gca gtg ctt gac gca ggc cac tca gtg tcc acc ctg				8125
Asp Leu Gly Gln Ala Val Leu Asp Ala Gly His Ser Val Ser Thr Leu				
	2675	2680	2685	
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Glu Lys Thr Leu Pro Gln Leu Leu Ala Lys Leu Ser Ile Leu Glu Asn				
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Arg Gly Val His Asn Ala Ser Leu Ala Leu Ser Ala Ser Ile Gly Arg				
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Val Arg Glu Leu Ile Ala Gln Ala Arg Gly Ala Ala Ser Lys Val Lys				
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<210> 36

<211> 2743

<212> PRT

<213> Homo sapiens

<400> 36

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			20					25						30	
Ala	Arg	Ala	Arg	Glu	Glu	Ala	Gly	Gly	Gly	Phe	Ser	Leu	His	Pro	Pro
			35				40						45		
Tyr	Phe	Asn	Leu	Ala	Glu	Gly	Ala	Arg	Ile	Ala	Ala	Ser	Ala	Thr	Cys
	50					55					60				
Gly	Glu	Glu	Ala	Pro	Ala	Arg	Gly	Ser	Pro	Arg	Pro	Thr	Glu	Asp	Leu
	65				70					75					80
Tyr	Cys	Lys	Leu	Val	Gly	Gly	Pro	Val	Ala	Gly	Gly	Asp	Pro	Asn	Gln
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Thr	Ile	Arg	Gly	Gln	Tyr	Cys	Asp	Ile	Cys	Thr	Ala	Ala	Asn	Ser	Asn
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Lys	Ala	His	Pro	Ala	Ser	Asn	Ala	Ile	Asp	Gly	Thr	Glu	Arg	Trp	Trp
		115					120					125			
Gln	Ser	Pro	Pro	Leu	Ser	Arg	Gly	Leu	Glu	Tyr	Asn	Glu	Val	Asn	Val
		130				135					140				
Thr	Leu	Asp	Leu	Gly	Gln	Val	Phe	His	Val	Ala	Tyr	Val	Leu	Ile	Lys
	145				150					155					160
Phe	Ala	Asn	Ser	Pro	Arg	Pro	Asp	Leu	Trp	Val	Leu	Glu	Arg	Ser	Met
				165					170						175

Asp Phe Gly Arg Thr Tyr Gln Pro Trp Gln Phe Phe Ala Ser Ser Lys
 180 185 190
 Arg Asp Cys Leu Glu Arg Phe Gly Pro Gln Thr Leu Glu Arg Ile Thr
 195 200 205
 Arg Asp Asp Ala Ala Ile Cys Thr Thr Glu Tyr Ser Arg Ile Val Pro
 210 215 220
 Leu Glu Asn Gly Glu Ile Val Val Ser Leu Val Asn Gly Arg Pro Gly
 225 230 235 240
 Ala Met Asn Phe Ser Tyr Ser Pro Leu Leu Arg Glu Phe Thr Lys Ala
 245 250 255
 Thr Asn Val Arg Leu Arg Phe Leu Arg Thr Asn Thr Leu Leu Gly His
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 Leu Met Gly Lys Ala Leu Arg Asp Pro Thr Val Thr Arg Arg Tyr Tyr
 275 280 285
 Tyr Ser Ile Lys Asp Ile Ser Ile Gly Gly Arg Cys Val Cys His Gly
 290 295 300
 His Ala Asp Ala Cys Asp Ala Lys Asp Pro Thr Asp Pro Phe Arg Leu
 305 310 315 320
 Gln Cys Thr Cys Gln His Asn Thr Cys Gly Gly Thr Cys Asp Arg Cys
 325 330 335
 Cys Pro Gly Phe Asn Gln Gln Pro Trp Lys Pro Ala Thr Ala Asn Ser
 340 345 350
 Ala Asn Glu Cys Gln Ser Cys Asn Cys Tyr Gly His Ala Thr Asp Cys
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 Tyr Tyr Asp Pro Glu Val Asp Arg Arg Arg Ala Ser Gln Ser Leu Asp
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 Gly Thr Tyr Gln Gly Gly Gly Val Cys Ile Asp Cys Gln His His Thr
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 Ala Gly Val Asn Cys Glu Arg Cys Leu Pro Gly Phe Tyr Arg Ser Pro
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 Asn His Pro Leu Asp Ser Pro His Val Cys Arg Arg Cys Asn Cys Glu
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 Ser Asp Phe Thr Asp Gly Thr Cys Glu Asp Leu Thr Gly Arg Cys Tyr
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 Cys Arg Pro Asn Phe Ser Gly Glu Arg Cys Asp Val Cys Ala Glu Gly
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 Phe Thr Gly Phe Pro Ser Cys Tyr Pro Thr Pro Ser Ser Ser Asn Asp
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 Ser Pro Gly Val Ala Asp Asp Arg Cys Asp Pro Asp Thr Gly Gln Cys
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 Arg Cys Arg Val Gly Phe Glu Gly Ala Thr Cys Asp Arg Cys Ala Pro
 565 570 575
 Gly Tyr Phe His Phe Pro Leu Cys Gln Leu Cys Gly Cys Ser Pro Ala
 580 585 590
 Gly Thr Leu Pro Glu Gly Cys Asp Glu Ala Gly Arg Cys Leu Cys Gln
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 Gly Phe Pro Asn Cys Gln Ala Cys Thr Cys Asp Pro Arg Gly Ala Leu
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 690 695 700
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 755 760 765
 Asn Pro Glu Gly Cys Thr Arg Cys Ser Cys Asp Leu Arg Gly Thr Leu
 770 775 780
 Gly Gly Val Ala Glu Cys Gln Pro Gly Thr Gly Gln Cys Phe Cys Lys
 785 790 795 800
 Pro His Val Cys Gly Gln Ala Cys Ala Ser Cys Lys Asp Gly Phe Phe
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 Gly Leu Asp Gln Ala Asp Tyr Phe Gly Cys Arg Ser Cys Arg Cys Asp

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Ile	Gly	Gly	Ala	Leu	Gly	Gln	Ser	Cys	Glu	Pro	Arg	Thr	Gly	Val	Cys				
		835					840					845							
Arg	Cys	Arg	Pro	Asn	Thr	Gln	Gly	Pro	Thr	Cys	Ser	Glu	Pro	Ala	Arg				
	850					855					860								
Asp	His	Tyr	Leu	Pro	Asp	Leu	His	His	Leu	Arg	Leu	Glu	Leu	Glu	Glu				
865					870					875					880				
Ala	Ala	Thr	Pro	Glu	Gly	His	Ala	Val	Arg	Phe	Gly	Phe	Asn	Pro	Leu				
				885					890					895					
Glu	Phe	Glu	Asn	Phe	Ser	Trp	Arg	Gly	Tyr	Ala	Gln	Met	Ala	Pro	Val				
			900					905					910						
Gln	Pro	Arg	Ile	Val	Ala	Arg	Leu	Asn	Leu	Thr	Ser	Pro	Asp	Leu	Phe				
		915					920					925							
Trp	Leu	Val	Phe	Arg	Tyr	Val	Asn	Arg	Gly	Ala	Met	Ser	Val	Ser	Gly				
	930					935					940								
Arg	Val	Ser	Val	Arg	Glu	Glu	Gly	Arg	Ser	Ala	Ala	Cys	Ala	Asn	Cys				
945					950					955					960				
Thr	Ala	Gln	Ser	Gln	Pro	Val	Ala	Phe	Pro	Pro	Ser	Thr	Glu	Pro	Ala				
				965					970					975					
Phe	Ile	Thr	Val	Pro	Gln	Arg	Gly	Phe	Gly	Glu	Pro	Phe	Val	Leu	Asn				
			980					985					990						
Pro	Gly	Thr	Trp	Ala	Leu	Arg	Val	Glu	Ala	Glu	Gly	Val	Leu	Leu	Asp				
		995					1000					1005							
Tyr	Val	Val	Leu	Leu	Pro	Ser	Ala	Tyr	Tyr	Glu	Ala	Ala	Leu	Leu	Gln				
1010					1015					1020									
Leu	Arg	Val	Thr	Glu	Ala	Cys	Thr	Tyr	Arg	Pro	Ser	Ala	Gln	Gln	Ser				
1025					1030					1035					1040				
Gly	Asp	Asn	Cys	Leu	Leu	Tyr	Thr	His	Leu	Pro	Leu	Asp	Gly	Phe	Pro				
			1045					1050						1055					
Ser	Ala	Ala	Gly	Leu	Glu	Ala	Leu	Cys	Arg	Gln	Asp	Asn	Ser	Leu	Pro				
		1060						1065					1070						
Arg	Pro	Cys	Pro	Thr	Glu	Gln	Leu	Ser	Pro	Ser	His	Pro	Pro	Leu	Ile				
	1075						1080					1085							
Thr	Cys	Thr	Gly	Ser	Asp	Val	Asp	Val	Gln	Leu	Gln	Val	Ala	Val	Pro				
	1090					1095					1100								
Gln	Pro	Gly	Arg	Tyr	Ala	Leu	Val	Val	Glu	Tyr	Ala	Asn	Glu	Asp	Ala				
1105					1110				1115					1120					
Arg	Gln	Glu	Val	Gly	Val	Ala	Val	His	Thr	Pro	Gln	Arg	Ala	Pro	Gln				
			1125						1130					1135					
Gln	Gly	Leu	Leu	Ser	Leu	His	Pro	Cys	Leu	Tyr	Ser	Thr	Leu	Cys	Arg				
		1140						1145					1150						

Gly Thr Ala Arg Asp Thr Gln Asp His Leu Ala Val Phe His Leu Asp
 1155 1160 1165
 Ser Glu Ala Ser Val Arg Leu Thr Ala Glu Gln Ala Arg Phe Phe Leu
 1170 1175 1180
 His Gly Val Thr Leu Val Pro Ile Glu Glu Phe Ser Pro Glu Phe Val
 1185 1190 1195 1200
 Glu Pro Arg Val Ser Cys Ile Ser Ser His Gly Ala Phe Gly Pro Asn
 1205 1210 1215
 Ser Ala Ala Cys Leu Pro Ser Arg Phe Pro Lys Pro Pro Gln Pro Ile
 1220 1225 1230
 Ile Leu Arg Asp Cys Gln Val Ile Pro Leu Pro Pro Gly Leu Pro Leu
 1235 1240 1245
 Thr His Ala Gln Asp Leu Thr Pro Ala Thr Ser Pro Ala Gly Pro Arg
 1250 1255 1260
 Pro Arg Pro Pro Thr Ala Val Asp Pro Asp Ala Glu Pro Thr Leu Leu
 1265 1270 1275 1280
 Arg Glu Pro Gln Ala Thr Val Val Phe Thr Thr His Val Pro Thr Leu
 1285 1290 1295
 Gly Arg Tyr Ala Phe Leu Leu His Gly Tyr Gln Pro Ala His Pro Thr
 1300 1305 1310
 Phe Pro Val Glu Val Leu Ile Asn Ala Gly Arg Val Trp Gln Gly His
 1315 1320 1325
 Ala Asn Ala Ser Phe Cys Pro His Gly Tyr Gly Cys Arg Thr Leu Val
 1330 1335 1340
 Val Cys Glu Gly Gln Ala Leu Leu Asp Val Thr His Ser Glu Leu Thr
 1345 1350 1355 1360
 Val Thr Val Arg Val Pro Glu Gly Arg Trp Leu Trp Leu Asp Tyr Val
 1365 1370 1375
 Leu Val Val Pro Glu Asn Val Tyr Ser Phe Gly Tyr Leu Arg Glu Glu
 1380 1385 1390
 Pro Leu Asp Lys Ser Tyr Asp Phe Ile Ser His Cys Ala Ala Gln Gly
 1395 1400 1405
 Tyr His Ile Ser Pro Ser Ser Ser Ser Leu Phe Cys Arg Asn Ala Ala
 1410 1415 1420
 Ala Ser Leu Ser Leu Phe Tyr Asn Asn Gly Ala Arg Pro Cys Gly Cys
 1425 1430 1435 1440
 His Glu Val Gly Ala Thr Gly Pro Thr Cys Glu Pro Phe Gly Gly Gln
 1445 1450 1455
 Cys Pro Cys His Ala His Val Ile Gly Arg Asp Cys Ser Arg Cys Ala
 1460 1465 1470

Thr Gly Tyr Trp Gly Phe Pro Asn Cys Arg Pro Cys Asp Cys Gly Ala
 1475 1480 1485

Arg Leu Cys Asp Glu Leu Thr Gly Gln Cys Ile Cys Pro Pro Arg Thr
 1490 1495 1500

Ile Pro Pro Asp Cys Leu Leu Cys Gln Pro Gln Thr Phe Gly Cys His
 1505 1510 1515 1520

Pro Leu Val Gly Cys Glu Glu Cys Asn Cys Ser Gly Pro Gly Ile Gln
 1525 1530 1535

Glu Leu Thr Asp Pro Thr Cys Asp Thr Asp Ser Gly Gln Cys Lys Cys
 1540 1545 1550

Arg Pro Asn Val Thr Gly Arg Arg Cys Asp Thr Cys Ser Pro Gly Phe
 1555 1560 1565

His Gly Tyr Pro Arg Cys Arg Pro Cys Asp Cys His Glu Ala Gly Thr
 1570 1575 1580

Ala Pro Gly Val Cys Asp Pro Leu Thr Gly Gln Cys Tyr Cys Lys Glu
 1585 1590 1595 1600

Asn Val Gln Gly Pro Lys Cys Asp Gln Cys Ser Leu Gly Thr Phe Ser
 1605 1610 1615

Leu Asp Ala Ala Asn Pro Lys Gly Cys Thr Arg Cys Phe Cys Phe Gly
 1620 1625 1630

Ala Thr Glu Arg Cys Arg Ser Ser Ser Tyr Thr Arg Gln Glu Phe Val
 1635 1640 1645

Asp Met Glu Gly Trp Val Leu Leu Ser Thr Asp Arg Gln Val Val Pro
 1650 1655 1660

His Glu Arg Gln Pro Gly Thr Glu Met Leu Arg Ala Asp Leu Arg His
 1665 1670 1675 1680

Val Pro Glu Ala Val Pro Glu Ala Phe Pro Glu Leu Tyr Trp Gln Ala
 1685 1690 1695

Pro Pro Ser Tyr Leu Gly Asp Arg Val Ser Ser Tyr Gly Gly Thr Leu
 1700 1705 1710

Arg Tyr Glu Leu His Ser Glu Thr Gln Arg Gly Asp Val Phe Val Pro
 1715 1720 1725

Met Glu Ser Arg Pro Asp Val Val Leu Gln Gly Asn Gln Met Ser Ile
 1730 1735 1740

Thr Phe Leu Glu Pro Ala Tyr Pro Thr Pro Gly His Val His Arg Gly
 1745 1750 1755 1760

Gln Leu Gln Leu Val Glu Gly Asn Phe Arg His Thr Glu Thr Arg Asn
 1765 1770 1775

Thr Val Ser Arg Glu Glu Leu Met Met Val Leu Ala Ser Leu Glu Gln
 1780 1785 1790

Leu Gln Ile Arg Ala Leu Phe Ser Gln Ile Ser Ser Ala Val Ser Leu

1795				1800				1805							
Arg	Arg	Val	Ala	Leu	Glu	Val	Ala	Ser	Pro	Ala	Gly	Gln	Gly	Ala	Leu
1810				1815				1820							
Ala	Ser	Asn	Val	Glu	Leu	Cys	Leu	Cys	Pro	Ala	Ser	Tyr	Arg	Gly	Asp
1825				1830				1835				1840			
Ser	Cys	Gln	Glu	Cys	Ala	Pro	Gly	Phe	Tyr	Arg	Asp	Val	Lys	Gly	Leu
1845				1850				1855							
Phe	Leu	Gly	Arg	Cys	Val	Pro	Cys	Gln	Cys	His	Gly	His	Ser	Asp	Arg
1860				1865				1870							
Cys	Leu	Pro	Gly	Ser	Gly	Val	Cys	Val	Asp	Cys	Gln	His	Asn	Thr	Glu
1875				1880				1885							
Gly	Ala	His	Cys	Glu	Arg	Cys	Gln	Ala	Gly	Phe	Met	Ser	Ser	Arg	Asp
1890				1895				1900							
Asp	Pro	Ser	Ala	Pro	Cys	Val	Ser	Cys	Pro	Cys	Pro	Leu	Ser	Val	Pro
1905				1910				1915				1920			
Ser	Asn	Asn	Phe	Ala	Glu	Gly	Cys	Val	Leu	Arg	Gly	Gly	Arg	Thr	Gln
1925				1930				1935							
Cys	Leu	Cys	Lys	Pro	Gly	Tyr	Ala	Gly	Ala	Ser	Cys	Glu	Arg	Cys	Ala
1940				1945				1950							
Pro	Gly	Phe	Phe	Gly	Asn	Pro	Leu	Val	Leu	Gly	Ser	Ser	Cys	Gln	Pro
1955				1960				1965							
Cys	Asp	Cys	Ser	Gly	Asn	Gly	Asp	Pro	Asn	Leu	Leu	Phe	Ser	Asp	Cys
1970				1975				1980							
Asp	Pro	Leu	Thr	Gly	Ala	Cys	Arg	Gly	Cys	Leu	Arg	His	Thr	Thr	Gly
1985				1990				1995				2000			
Pro	Arg	Cys	Glu	Ile	Cys	Ala	Pro	Gly	Phe	Tyr	Gly	Asn	Ala	Leu	Leu
2005				2010				2015							
Pro	Gly	Asn	Cys	Thr	Arg	Cys	Asp	Cys	Thr	Pro	Cys	Gly	Thr	Glu	Ala
2020				2025				2030							
Cys	Asp	Pro	His	Ser	Gly	His	Cys	Leu	Cys	Lys	Ala	Gly	Val	Thr	Gly
2035				2040				2045							
Arg	Arg	Cys	Asp	Arg	Cys	Gln	Glu	Gly	His	Phe	Gly	Phe	Asn	Gly	Cys
2050				2055				2060							
Gly	Gly	Cys	Arg	Pro	Cys	Ala	Cys	Gly	Pro	Ala	Ala	Glu	Gly	Ser	Glu
2065				2070				2075				2080			
Cys	His	Pro	Gln	Ser	Gly	Gln	Cys	His	Cys	Arg	Pro	Gly	Thr	Met	Gly
2085				2090				2095							
Pro	Gln	Cys	Arg	Glu	Cys	Ala	Pro	Gly	Tyr	Trp	Gly	Leu	Pro	Glu	Gln
2100				2105				2110							
Gly	Cys	Arg	Arg	Cys	Gln	Cys	Pro	Gly	Gly	Arg	Cys	Asp	Pro	His	Thr
2115				2120				2125							

Gly Arg Cys Asn Cys Pro Pro Gly Leu Ser Gly Glu Arg Cys Asp Thr
 2130 2135 2140

Cys Ser Gln Gln His Gln Val Pro Val Pro Gly Gly Pro Val Gly His
 2145 2150 2155 2160

Ser Ile His Cys Glu Val Cys Asp His Cys Val Val Leu Leu Leu Asp
 2165 2170 2175

Asp Leu Glu Arg Ala Gly Ala Leu Leu Pro Ala Ile His Glu Gln Leu
 2180 2185 2190

Arg Gly Ile Asn Ala Ser Ser Met Ala Trp Ala Arg Leu His Arg Leu
 2195 2200 2205

Asn Ala Ser Ile Ala Asp Leu Gln Ser Gln Leu Arg Ser Pro Leu Gly
 2210 2215 2220

Pro Arg His Glu Thr Ala Gln Gln Leu Glu Val Leu Glu Gln Gln Ser
 2225 2230 2235 2240

Thr Ser Leu Gly Gln Asp Ala Arg Arg Leu Gly Gly Gln Ala Val Gly
 2245 2250 2255

Thr Arg Asp Gln Ala Ser Gln Leu Leu Ala Gly Thr Glu Ala Thr Leu
 2260 2265 2270

Gly His Ala Lys Thr Leu Leu Ala Ala Ile Arg Ala Val Asp Arg Thr
 2275 2280 2285

Leu Ser Glu Leu Met Ser Gln Thr Gly His Leu Gly Leu Ala Asn Ala
 2290 2295 2300

Ser Ala Pro Ser Gly Glu Gln Leu Leu Arg Thr Leu Ala Glu Val Glu
 2305 2310 2315 2320

Arg Leu Leu Trp Glu Met Arg Ala Arg Asp Leu Gly Ala Pro Gln Ala
 2325 2330 2335

Ala Ala Glu Ala Glu Leu Ala Ala Ala Gln Arg Leu Leu Ala Arg Val
 2340 2345 2350

Gln Glu Gln Leu Ser Ser Leu Trp Glu Glu Asn Gln Ala Leu Ala Thr
 2355 2360 2365

Gln Thr Arg Asp Arg Leu Ala Gln His Glu Ala Gly Leu Met Asp Leu
 2370 2375 2380

Arg Glu Ala Leu Asn Arg Ala Val Asp Ala Thr Arg Glu Ala Gln Glu
 2385 2390 2395 2400

Leu Asn Ser Arg Asn Gln Glu Arg Leu Glu Glu Ala Leu Gln Arg Lys
 2405 2410 2415

Gln Glu Leu Ser Arg Asp Asn Ala Thr Leu Gln Ala Thr Leu His Ala
 2420 2425 2430

Ala Arg Asp Thr Leu Ala Ser Val Phe Arg Leu Leu His Ser Leu Asp
 2435 2440 2445

Gln Ala Lys Glu Glu Leu Glu Arg Leu Ala Ala Ser Leu Asp Gly Ala
 2450 2455 2460

Arg Thr Pro Leu Leu Gln Arg Met Gln Thr Phe Ser Pro Ala Gly Ser
 2465 2470 2475 2480

Lys Leu Arg Leu Val Glu Ala Ala Glu Ala His Ala Gln Gln Leu Gly
 2485 2490 2495

Gln Leu Ala Leu Asn Leu Ser Ser Ile Ile Leu Asp Val Asn Gln Asp
 2500 2505 2510

Arg Leu Thr Gln Arg Ala Ile Glu Ala Ser Asn Ala Tyr Ser Arg Ile
 2515 2520 2525

Leu Gln Ala Val Gln Ala Ala Glu Asp Ala Ala Gly Gln Ala Leu Gln
 2530 2535 2540

Gln Ala Asp His Thr Trp Ala Thr Val Val Arg Gln Gly Leu Val Asp
 2545 2550 2555 2560

Arg Ala Gln Gln Leu Leu Ala Asn Ser Thr Ala Leu Glu Glu Ala Met
 2565 2570 2575

Leu Gln Glu Gln Gln Arg Leu Gly Leu Val Trp Ala Ala Leu Gln Gly
 2580 2585 2590

Ala Arg Thr Gln Leu Arg Asp Val Arg Ala Lys Lys Asp Gln Leu Glu
 2595 2600 2605

Ala His Ile Gln Ala Ala Gln Ala Met Leu Ala Met Asp Thr Asp Glu
 2610 2615 2620

Thr Ser Lys Lys Ile Ala His Ala Lys Ala Val Ala Ala Glu Ala Gln
 2625 2630 2635 2640

Asp Thr Ala Thr Arg Val Gln Ser Gln Leu Gln Ala Met Gln Glu Asn
 2645 2650 2655

Val Glu Arg Trp Gln Gly Gln Tyr Glu Gly Leu Arg Gly Gln Asp Leu
 2660 2665 2670

Gly Gln Ala Val Leu Asp Ala Gly His Ser Val Ser Thr Leu Glu Lys
 2675 2680 2685

Thr Leu Pro Gln Leu Leu Ala Lys Leu Ser Ile Leu Glu Asn Arg Gly
 2690 2695 2700

Val His Asn Ala Ser Leu Ala Leu Ser Ala Ser Ile Gly Arg Val Arg
 2705 2710 2715 2720

Glu Leu Ile Ala Gln Ala Arg Gly Ala Ala Ser Lys Val Lys Val Pro
 2725 2730 2735

Met Lys Phe Asn Gly Arg Ser
 2740