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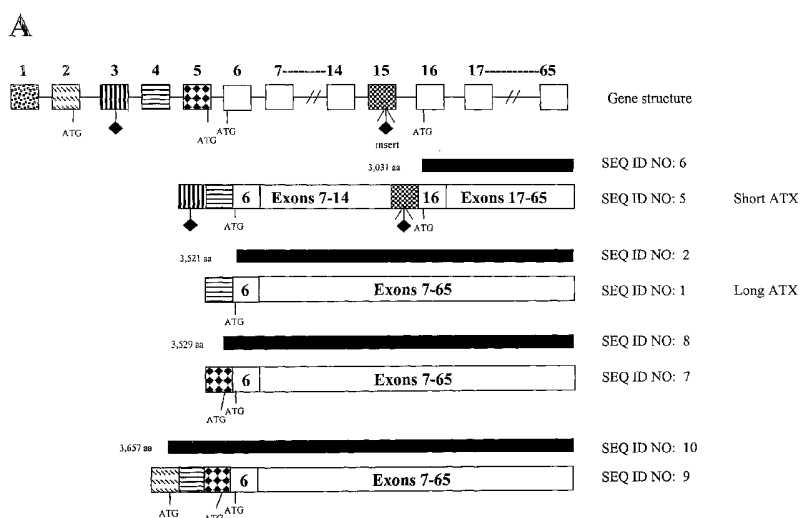
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(54) Title: ATM RELATED KINASE ATX, NUCLEIC ACIDS ENCODING SAME AND METHODS OF USE



(57) **Abstract:** The invention provides an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1. Also provided is an isolated oligonucleotide having at least 15 contiguous nucleotides of a nucleotide sequence referenced as SEQ ID NO:11. An isolated polypeptide having substantially the same amino acid sequence as SEQ ID NO:2 is further provided as well as an antibody, or antigen binding fragment thereof, which specifically binds to an ATX polypeptide and has an amino acid sequence as referenced in SEQ ID NO:2. A method for identifying an ATX-modulatory compound is additionally provided. The method consists of measuring the level of an ATX polypeptide in the presence of a test compound, wherein a difference in the level of said ATX polypeptide in the presence of said test compound compared to in the absence of said test compound indicating that said test compound is an ATX-modulatory compound, and wherein said ATX-modulatory compound is not caffeine or wortmannin.



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

ATM RELATED KINASE ATX, NUCLEIC ACIDS ENCODING SAME AND
METHODS OF USE

5 This invention was made with government support
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certain rights in this invention.

BACKGROUND OF THE INVENTION

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 This invention relates generally to the fields
of molecular biology and molecular medicine and more
specifically to the identification of phosphoinositide
3-kinase related kinases (PIKKs) involved in cell cycle
15 control and mRNA surveillance pathways.

20

 The mitotic cell cycle is the process by which
a cell creates an exact copy of its chromosomes and then
segregates each copy into two cells. The sequence of
events of the cell cycle is regulated such that cell
division does not occur until the cell has completed
accurate DNA replication. To ensure that cells pass
accurate copies of their genomes on to the next
generation, evolution has overlaid the core cell cycle
25 machinery with a series of surveillance pathways termed
cell cycle checkpoints. The overall function of these
checkpoints is to detect damaged or abnormally structured
DNA, and to coordinate cell cycle progression with DNA
repair.

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 Members of the phosphoinositide 3-kinase
related kinases (PIKK) family of kinases are involved in
cell cycle checkpoints and DNA damage repair. The PIKK
family members identified to date express a

carboxylterminal domain that displays significant sequence homology to the catalytic domains of phosphoinositide (PI) 3-kinases. Indeed, many, but not all of the PIKKs have been shown to possess protein serine-threonine kinase activities (McMahon et al., Cell 94:363-374 (1998); Vassilev et al., Cell 2:869-875 (1998); Grant et al., Cell 2:863-867 (1998); Hunter, Cell 83:1-4 (1995); Tibbetts and Abraham, Signaling Networks and Cell Cycle: Themolecular Basis of Cancer and Other Diseases pp. 267-301 (2000)). In mammalian cells, three PIKK family members, ATM, ATR, and DNA-dependent protein kinase (DNA-PK), serve as proximal signal transducers in cell-cycle checkpoint and DNA repair pathways (Abraham, Genes & Dev. 15:2177-2196 (2001); Durocher and Jackson, Curr. Opin. Cell Biol. 13:2225-231 (2001)). The critical roles of ATM in orchestrating cellular responses to various forms of stress are underscored by the diverse pathologies associated with the hereditary disorder, ataxiatelangiectasia (A-T) (Crawford, Seminarsin Ped. Neuro. 5:287-294 (1998); Rotman and Shiloh, Human Mol. Gen. 7:1555-1563 (1998); Rotman and Shiloh, Oncogene 18:6135-6144 (1999)). A-T patients lack functional ATM and develop symptoms including extreme sensitivity to irradiation, cerebellar degeneration, oculocutaneous telangiectasias, gonadal deficiencies, immunodeficiencies, and increased risk of cancer (Lehman and Carr, Trends in Genet. 11:375-377 (1995)). Fibroblasts derived from these patients show defects in cell cycle checkpoints and are defective in their response to irradiation (Painter and Young, Proc. Natl. Acad. Sci. (USA) 77:7315-7317 (1980)).

In general, the proteins in the PIKK family of kinases play important roles in mRNA surveillance and cell cycle progression in order to insure genetic

integrity from generation to generation. Compounds that modulate PIKK polypeptides can result in altered progression through the cell cycle leading to increased or decreased cell survival. For example, a
5 PIKK-modulatory compound can make a cell more or less susceptible to cell death in the presence of radiation or a cytotoxic agent.

All cancer cells have a dysfunctional cell
10 cycle and continue through the cell cycle in an inappropriate manner, either by failing to respond to negative growth signals or by failing to die in response to the appropriate signal. In addition, most cancer cells lack genomic integrity and often have an increased
15 chromosome count compared to normal cells. Therefore, compounds that inhibit cell cycle checkpoints or DNA damage repair, in combination with the cytotoxic agents, can cause cancer cell death by forcing cancer cells to progress through the cell cycle in the presence of DNA
20 damaging agents such that they undergo events that lead to cell death.

Thus, there exists a need to identify additional members of the PIKK family of kinases and
25 compounds that modulate these kinases. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

30 The invention provides an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1. Also provided is an isolated oligonucleotide having at least 15 contiguous nucleotides
35 of a nucleotide sequence referenced as SEQ ID NO:11. An

isolated polypeptide having substantially the same amino acid sequence as SEQ ID NO:2 is further provided as well as an antibody, or antigen binding fragment thereof, which specifically binds to an ATX polypeptide and has an amino acid sequence as referenced in SEQ ID NO:2. A method for identifying an ATX-modulatory compound is additionally provided. The method consists of measuring the level of an ATX polypeptide in the presence of a test compound, wherein a difference in the level of said ATX polypeptide in the presence of said test compound compared to in the absence of said test compound indicating that said test compound is an ATX-modulatory compound, and wherein said ATX-modulatory compound is not caffeine or wortmannin.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows the genomic structure of the ATX locus along with clones isolated to date. The black diamonds denote the locations of translational stop codons and black bars indicate open reading frames that give rise to various ATX polypeptides. The lines and symbols below exon 15 indicate an allelic variant that contains a 27 bp insertion having two in-frame stop codons. Figure 1B shows the location of N-terminal homology 1 (NH1), NH2, PI3-K catalytic (PI3-Kc), PKC- λ/ι -interacting protein (LIP), and FAT-C (C) domains. The numbers shown indicate % identity/similarity and shading highlights amino acid identity with ATX. A sequence alignment of the PI 3-Kc domains of ATX, CeSMG-1, mTOR, and ATM is shown. Figure 1C shows immune complex kinase assays with GST-p53₁₋₇₀, GST-p53₁₋₇₀(S15A), or with GSThUpf11019-1118 as substrates. The reaction products were immunoblotted with α -HA (lower panel).

Figure 1D shows immune complex assays with cells or α -HA-ATX immunoprecipitates treated with wortmannin.

Figure 2A shows clonogenic survival assays after UV exposure. Figure 2B shows clonogenic survival assays after IR exposure. The upper panel displays colony outgrowth results from cells transfected with the indicated plasmids, and not exposed to IR. Figure 2C shows clonogenic survival assays of cells treated with ATX-directed antisense oligonucleotides (AS). The right panel displays colony survival results from non-irradiated cells treated with the indicated oligonucleotides.

Figure 3A shows whole cell extracts resolved by SDS-PAGE and sequentially immunoblotted with the indicated antibodies. Figure 3B shows extracts of transfected cells separated by SDS-PAGE and sequentially immunoblotted with the indicated antibodies. The p53 phosphoserine-15 specific antibody is designated α -pSer15. Figure 3C shows extracts of cells treated with S or AS oligonucleotides and analyzed as described in panel A. Figure 3D shows cell cycle progression in AS-transfected cells examined by flow cytometry. The table shows the percentages of cells in each cell cycle phase. The right panel shows immunoblot analyses from the same cell population. Figure 3E shows an effect of caffeine on AS-induced cell cycle defects. The table shows percentages of cells in each cell-cycle phase, plus the ratio of G2/M to G1 cells for each sample. The right panel shows immunoblotting results from the same cell populations.

Figure 4A shows an effect of ATX overexpression on basal viability. Cell densities of the scanned images

from each sample were obtained with the ImagePro Plus software program. Figure 4B shows an effect of ATX overexpression on radiosensitivity. Surviving cells were quantitated as described in panel except that arbitrary unit values for each group were normalized to the
5 corresponding nonirradiated control.

Figure 5A shows cells transfected with GAL4 or GAL4-hUpf11019-1118 expression constructs with the
10 indicated samples treated with wortmannin. The right panel shows phosphatase treatment. The soluble proteins were separated by SDS-PAGE and immunoblotted with α -GAL4 mAb. The arrow indicates the uppermost band of the phosphorylated GAL4-hUpf11019-1118 reporter protein.
15 Figure 5B shows an effect of ATMKI or ATXKI expression on UV stimulation of GAL4-hUpf1 phosphorylation.

Figure 6A shows an effect of HA-ATXKI or HAATMKI expression on NMD. Nuclear RNA was isolated from
20 transfected cells and β -globin and MUP mRNAs were quantitated by RT-PCR and PhosphorImaging. For each pair of transfections, the level of Globin mRNA was normalized to the level of MUP mRNA and expressed below each lane as a percentage of the normalized level of Globin Norm mRNA,
25 which was defined as 100. Figure 6B shows an effect of ATX AS oligonucleotide on NMD.

Figure 7 shows the effect of small-interfering (si) RNA reduction of ATX on response to ionizing
30 radiation (IR). U20S cells transfected with si RNA directed against luciferase (control) or ATX were treated with different doses of ionizing radiation and lysed after 1 hour or 18 hours. Cellular extracts were separated by SDS-PAGE and immunoblotted with an
35 anti-phospho-Histone H2AX antibody. The level of a

control polypeptide, α -tubulin, is shown in the lower panel for comparison.

DETAILED DESCRIPTION OF THE INVENTION

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This invention is directed to isolated ATX nucleic acids and polypeptides. ATX is a novel PIKK kinase family member that participates in stress-induced p53 and cell cycle checkpoint activation in cells exposed to DNA damaging agents. In addition, ATX can activate the intrinsic non-sense mediated mRNA decay (NMD) pathway in these cells. The invention is also directed to methods of identifying ATX-modulatory compounds and using these compounds to modulate cell survival. Compounds that modulate cellular survival can be useful in the treatment of diseases characterized by excessive cell growth or excessive cell death.

In one embodiment, an expressed sequence tag (EST) with homology to a conserved region in the catalytic domains of PIKK family members was used to isolate a full-length cDNA encoding a novel member of the PIKK family, termed ATX. The ATX polypeptide was detected in both the nucleus and cytoplasm of human cells, and formed nuclear foci upon exposure to UV light. In addition, the cell cycle regulatory proteins p53 and hUpf1 were found to be phosphorylated by ATX. Furthermore, the reduction of endogenous ATX in a cell using anti-sense oligonucleotides resulted in decreased survival of cells, and decreased phosphorylation and stabilization of p53 in cells exposed to UV light. Similar to other PIKK family members, ATX activity was inhibited by wortmannin and caffeine.

As used herein, the term "ATX polypeptide" refers to a polypeptide with substantially the same amino acid sequence as that shown in SEQ ID NO:2 (human ATX). "Substantially the same amino acid sequence" is intended to mean an amino acid sequence contains a considerable degree of sequence identity or similarity, such as at least 70%, 80%, 90%, 95%, 98%, or 100% sequence identity or similarity, to a reference amino acid sequence. Substantially the same amino acid sequence includes conservative and non-conservative amino acid changes, gaps, and insertions to an amino acid sequence. Conservative and non-conservative amino acid changes, gaps, and insertions to an amino acid sequence can be compared to a reference sequence using available algorithms and programs such as the Smith-Waterman algorithm and the BLAST homology search program (Altschul et al., J. Mol. Biol. 215:403-410 (1990)).

It is understood that a fragment of ATX can be sufficient in order to produce an ATX activity. Activities associated with ATX include, for example, kinase activity, cell cycle checkpoint activity, and NMD activity. For example, fragments of ATX which retain substantially an activity of the entire polypeptide are included within the definition. Fragments can include, for example, amino terminal, carboxyl terminal, or internal deletions of a full length ATX polypeptide. In addition, fragments can include domains of a full length ATX polypeptide, such as for example, a kinase domain, NH1 domain, NH2 domain, or LIP domain. A fragment can contain, for example, at least about 10, 100, 500, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500 or more contiguous or non-contiguous amino acid residues of a full-length ATX polypeptide. ATX polypeptide fragments include the fragments described above, but excludes fragments

KIAA0421 (Accession number AB007881), KIAA0220 (Accession number D86974), and LIP (Accession number U32581), which are present in databases. Polypeptide fragments can be generated using a variety of methods. For example,
5 polypeptide fragments can be generated using recombinant DNA methods, enzymatic cleavage, or chemical cleavage of larger polypeptides.

It is understood that limited modifications to
10 the ATX polypeptide can be made without destroying an activity of ATX. For example, ATX is intended to include other ATX family members such as those polypeptides that are found to exhibit the above sequence homologies. Such members include, for example, homologs of ATX that can be
15 cloned from other organisms such as monkeys, cows, rats, mice, chickens, frogs, flies or worms. The sequence of possible homologs of human ATX are available in nucleotide databases.

20 Various modifications of the ATX primary amino acid sequence can result in polypeptides having substantially equivalent, decreased, or enhanced function as compared to the sequence set forth as SEQ ID NO:2. Those skilled in the art recognize that such
25 modifications can be desirable at times in order to enhance the bioactivity, bioavailability or stability of ATX, or to facilitate its synthesis or purification. Contemplated amino acid substitutions to the native sequence of ATX can include, for example, conservative
30 changes, wherein a substituted amino acid has similar structural or chemical properties such as replacement of a polar amino acid with another polar amino acid or replacement of a charged amino acid with a similarly charged amino acid. Those skilled in the art also
35 recognize that nonconservative changes such as

replacement of an uncharged polar amino acid with an non-polar amino acid or replacement of a charged amino acid with an uncharged polar amino acid, can also be made without affecting a function of ATX. In addition, a variety of polypeptide modifications are known in the art for constraining the structure of polypeptides to enhance stability or binding (Cabezas and Satterthwait, J. Am. Chem. Soc. 121:3862-3875 (1999); Stanfield et al., Structure 7:131-142 (1999)).

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A polypeptide can be modified by naturally occurring modifications such as post-translational modifications, including phosphorylation, lipidation, prenylation, sulfation, hydroxylation, acetylation, addition of carbohydrate, addition of prosthetic groups or cofactors, formation of disulfide bonds, proteolysis, assembly into macromolecular complexes, and the like. Chemical modifications of the polypeptide such as, for example, alkylation, acylation, carbamylation, and iodination can also be used to modify an ATX polypeptide. In addition, various molecules, such as other polypeptides, carbohydrates, or lipids, or small molecules can be attached to ATX including fragments of ATX. For example, ATX can contain a label moiety, a sequence such as a FLAG epitope, or be fused to another polypeptide such as a DNA binding domain.

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Those skilled in the art can determine which residues and which regions of a ATX sequence are likely to be tolerant of modification and still retain an activity associated with ATX. For example, amino acid substitutions or chemical or enzymatic modifications at residues that are less well conserved between species are more likely to be tolerated than substitutions at highly conserved residues. Accordingly, an alignment can be

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performed among ATX sequences of various species to determine residues and regions in which modifications are likely to be tolerated (Figure 1B). Additional guidance for determining residues and regions of ATX likely to be tolerant of modification is provided by studies of ATX fragments and variants. In addition, it can be useful to modify ATX in a way that destroys an activity associated with ATX. For example, as disclosed herein, the mutation of an aspartic acid to an alanine at conserved residue Asp-2195 in the ATX kinase domain generates a kinase-inactive version of ATX.

As used herein, the term "level" in reference to a level of an ATX nucleic acid or polypeptide refers to the amount, accumulation, or rate of synthesis of a molecule or to the amount or rate of an activity associated with the molecule. A level can be represented, for example, by the amount or synthesis rate of messenger RNA (mRNA) encoded by a gene, the amount or synthesis rate of polypeptide corresponding to a given amino acid sequence encoded by a gene, or the amount or synthesis rate of a biochemical form of a molecule accumulated in a cell, including, for example, the amount of particular post-synthetic modifications of a molecule such as a polypeptide or nucleic acid. In addition, a level can be represented, for example, by the extent of phosphorylation of a substrate molecule or by the amount of an activity such as cell cycle checkpoint activity, NMD activity or ability to induce cell death or cell survival. The term can be used to refer to an absolute amount of a molecule or activity in a sample or to a relative amount of the molecule or activity, including amounts and activities determined under steady-state or non-steady-state conditions. For example, the expression

level of a molecule can be determined relative to a control component molecule in a sample.

As used herein, the term "p53" is intended to mean a polypeptide with substantially the same amino acid sequence as that shown in SEQ ID NO:4 (human p53). As described above for ATX, it is understood that p53 includes fragments of the full length p53 polypeptide. For example, the amino terminal 70 amino acids of p53 (p53 1-70) can be used in the methods of the invention as a substrate for ATX kinase activity. Also, for example, a fragment of p53 that includes the LSQE sequence located at amino acids 14 to 17 of p53 can be used as a substrate for ATX kinase activity. In addition, as described above for ATX, a p53 polypeptide includes p53 from species other than humans, and includes modifications to the p53 polypeptide including conservative and non-conservative amino acid changes, post-translational modifications and chemical modification. Also, as described for ATX, a p53 polypeptide can contain additional sequences such as a known epitope or a label moiety.

The term "specifically binds" is intended to mean the molecule will have an affinity for the target molecule that is measurably higher than its affinity for a non-specific interaction. For example, a nucleic acid can specifically bind to another nucleic acid by complementary base pairing between the nucleotides. In addition, a polypeptide such as an antibody that specifically binds another polypeptide will have an affinity for the target polypeptide or antigen that is measurably higher than its affinity for a non-specific interaction. Furthermore, a compound such as a small organic molecule can specifically bind to a target molecule with an affinity that is measurably higher than

its affinity for a non-specific interaction. Binding affinity can be low or high affinity so long as the binding is sufficient to be detectable. For example, a compound can bind ATX with a binding affinity (Kd) of about 10^{-4} M or less, 10^{-5} M or less, 10^{-6} M or less, about 10^{-7} M or less, including about 10^{-8} M or less, such as 10^{-9} M or less. Several methods for detecting or measuring nucleotide, polypeptide, and other compound binding are well known in the art and disclosed herein.

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As used herein, the term "compound" is intended to mean an isolated macromolecule of natural or synthetic origin that can be assayed using the methods of the invention. A compound includes, for example, a polypeptide, peptidomimetic, non-peptidyl compound, carbohydrate, lipid, an antibody or antibody fragment, a small organic or inorganic molecule, or a nucleotide sequence including an aptamer, antisense oligonucleotide, interfering RNA or ribozyme. For example, a compound can be an isolated cDNA sequence. A compound can have a known or unknown structure. A compound can be isolated or be part of a population of compounds such as a library. For example, a compound can be a small organic compound obtained from a combinatorial chemical library. A library of compounds can be a random collection of compounds or can be rationally designed based on a physical characteristic. A compound which is assayed in the methods of the invention can be called a "test compound" and if the test compound has the ability to modulate the level of ATX it can be called an "ATX-modulatory compound." One compound or more than one compound can be used in the methods of the invention.

As used herein, a "stressor agent" is any agent that can induce a stress response pathway within a cell.

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Several stressor agents are known in the art such as UV light, ionizing radiation, reactive oxygen intermediates, cytotoxic agents, and replicational stress imposed by DNA replication inhibitors including, for example, hydroxyurea and aphidicolin. In addition, environmental conditions such as excessive heat can induce a stress response pathway within a cell resulting in, for example, the induction of heat shock proteins. Stress response pathways include DNA repair pathways, non-sense mediated mRNA decay (NMD), heat shock pathways, the induction of apoptosis, activation of the NFkB transcription factor, activation of the stress-activated MAP kinase pathways including, for example, JNK and p38 pathways, and activation of ubiquitin-dependent proteolysis.

As used herein, the term "non-sense mediated messenger RNA (mRNA) decay (NMD)" is intended to mean the surveillance mechanism within cells whereby imperfect mRNAs that contain premature translation termination codons are preferentially degraded. These imperfect mRNAs can result in polypeptides that are nonfunctional or have altered function such as gain-of function or dominant negative mutations.

As used herein, the term an "amount effective" or "effective amount" when used in reference to a compound that modulates cell survival or growth is intended to mean an amount of the compound or molecule sufficient to increase or decrease cell survival or growth. Modulation also includes induction of cell survival or growth or complete blockage of cell survival or growth. In addition, an effective amount of a compound is intended to mean an amount of the compound that is sufficient to treat or reduce the severity of a condition in an affected subject.

The invention provides an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1. In addition, the invention provides an isolated nucleic acid molecule having
5 substantially the same nucleotide sequence as SEQ ID NO:1 where the nucleic acid molecule encodes an ATX polypeptide containing an amino acid sequence shown in SEQ ID NO:2. For example, the invention provides an isolated nucleic acid molecule containing the sequence
10 shown in SEQ ID NO:1.

Substantially the same nucleic acid sequence is intended to mean a nucleic acid sequence contains a considerable degree of sequence identity or similarity,
15 such as at least 70%, 80%, 90%, 95%, 98%, or 100% sequence identity or similarity, to a reference nucleic acid sequence. Substantially the same nucleic acid sequence includes nucleic acid changes, gaps, and insertions to an nucleic sequence. Nucleic acid changes,
20 gaps, and insertions to a nucleic acid sequence can be compared to a reference sequence using available algorithms and programs such as the Smith-Waterman algorithm and the BLAST homology search program (Altschul et al., J. Mol. Biol. 215:403-410 (1990)).

25 Isolated nucleic acid molecules include DNA sequences and RNA transcripts, both sense and complementary anti-sense strands, including splice variants thereof encoding ATX polypeptides. An isolated
30 nucleic acid molecule can contain a double stranded molecules or single stranded molecules, including RNA as well as coding and noncoding DNA. DNA sequences of the invention include genomic and cDNA sequences as well as wholly or partially chemically synthesized DNA sequences.
35 Genomic DNA of the invention comprises the protein coding

region for a polypeptide of the invention and includes allelic variants of the preferred nucleic acid of the invention. Genomic DNA of the invention is distinguishable from genomic DNAs encoding polypeptides other than ATX in that it includes an ATX protein coding region found in ATX-encoding cDNA of the invention. Genomic DNA of the invention can be transcribed into RNA, and the resulting RNA transcript can undergo one or more splicing events wherein one or more introns of the transcript are removed, or "spliced out." Peptide nucleic acids (PNAs) encoding a polypeptide of the invention are also contemplated (Corey, TIBTech 15:224-229 (1997)). PNAs are DNA analogs containing neutral amide backbone linkages that are resistant to DNA degradation enzymes and which bind to complementary sequences at higher affinity than analogous DNA sequences as a result of the neutral charge on the backbone of the molecule.

RNA transcripts that can be spliced by alternative mechanisms, and therefore be subject to removal of different RNA sequences but still encode an ATX polypeptide, are referred to in the art as splice variants which are embraced by the invention. Splice variants comprehended by the invention therefore are encoded by the same DNA sequences but arise from distinct mRNA transcripts. Allelic variants are known in the art to be modified forms of a wild type gene sequence, the modification resulting from recombination during chromosomal segregation or exposure to conditions which give rise to genetic mutation. Allelic variants, like wild type genes, are inherently naturally occurring sequences (as opposed to non-naturally occurring variants which arise from *in vitro* manipulation).

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An allelic variant of ATX is disclosed herein as SEQ ID NO:5. This form of ATX is produced as the result of allelic variation in exon 15 which leads to the insertion of 27 nucleotides beginning at nucleotide 1427 (Figure 1A). This sequence alteration causes the insertion of two in-frame stop codons and the use of the next available ATG codon in exon 16 as the translational start site, resulting in an amino-terminally truncated or short form of ATX. A form of ATX that is similar to the long form of ATX disclosed herein (SEQ ID NO:1) is referenced as SEQ ID NO:7. This form of ATX has exon 5 spliced to exon 6 which results in a different N-terminus and 8 additional amino acids in the resulting polypeptide (Figure 1A). In the experiments disclosed herein clones that were isolated with exon 5 frequently contained exon 3 which place an in-frame stop codon at the 3' end of this DNA (Example 1). The longest form of ATX (SEQ ID NO:9) was isolated, however the exon 3 associated stop codon was present in this transcript as well.

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In addition to genomic DNA, isolated nucleic acids include cDNA. cDNA can be obtained through reverse transcription of an RNA nucleic acid encoding ATX, followed by second strand synthesis of a complementary strand to provide a double stranded DNA. In addition, nucleic acid molecules can be chemically synthesized meaning produced by purely chemical, as opposed to enzymatic, methods. Wholly chemically synthesized DNA sequences are produced entirely by chemical means, and partially synthesized DNAs are those where only portions of the resulting DNA were produced by chemical means.

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ATX nucleic acid molecules include homologs of the human ATX sequence. Species homologs in general share at least 50%, at least 60%, at least 70%, at least

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80%, at least 90%, at least 95% or at least 99% homology with a human DNA of the invention. ATX nucleic acids include species homologs of the human ATX sequence, but exclude a mouse EST that contains a sequence homologous to the 3' part of ATX is (GenBank Accession Number BC024431) and a *Macaca fascicularis* brain cDNA clone Qf1A-15747 (accession number AB056380).

The invention also provides anti-sense oligonucleotides based on SEQ ID NO:1. For example, the invention provides an isolated oligonucleotide having at least 15 contiguous nucleotides of the nucleotide sequence 5'-AGCAAGCTCCCTCCTGTCTC-3' (SEQ ID NO:11). The oligonucleotide shown in SEQ ID NO:11 is an ATX anti-sense oligonucleotide that has been shown herein to decrease the level of ATX in a cell (Example 5).

Nucleic acids of the invention also permit identification and isolation of nucleic acid encoding related ATX polypeptides by well known techniques including Southern hybridization, Northern hybridization, and polymerase chain reaction (PCR). Examples of related nucleic acids include human and non-human nucleic acid sequences, including allelic variants, as well as nucleic acids encoding polypeptides homologous to ATX and structurally related polypeptides sharing one or more biological, immunological, or physical properties of ATX.

The invention provides a method for detecting an ATX nucleic acid molecule in a sample, by contacting the sample with an ATX nucleic acid molecule under conditions that allow specific hybridization to ATX nucleic acid, and detecting the specific hybridization. In addition, the invention provides a method for detecting an ATX nucleic acid molecule in a sample, by

contacting a nucleic acid fraction derived from the sample with a PCR primer pair set under conditions that allow amplification of an ATX nucleic acid, and detecting amplified ATX nucleic acid. Kits for detecting ATX
5 nucleic acids based on these methods are provided as well.

Fragments of ATX nucleic acid molecules are useful in the invention, for example, as probes for
10 detection of full length or other fragment ATX nucleic acids. A nucleic acid fragment can include for example 5', 3', or internal deletions of a full length ATX nucleic acid sequence. For example, the invention provides an isolated ATX nucleic acid molecule as
15 referenced in SEQ ID NO:5. Alternatively, the invention provides ATX nucleic acid fragments other than the fragment as referenced in SEQ ID NO:5. For example, the invention provides ATX nucleic acid fragments that contain carboxyl terminal deletions of a full length ATX
20 polypeptide. In addition, fragments can include domains of a full length ATX nucleic acid sequence, for example, a kinase domain, NH1 domain, NH2 domain, or LIP domain. A fragment can contain, for example, at least about 10, 100, 1,000, 2,500, 5,000, 7,500, 10,000, 12,500 or more
25 contiguous or non-contiguous nucleic acid residues of a full-length ATX nucleic acid sequence. ATX nucleic acid fragments include the fragments described above, but excludes fragments KIAA0421 (Accession number AB007881), KIAA0220 (Accession number D86974), and LIP (Accession
30 number U32581), which are present in databases. One or more fragment nucleic acids can be included in kits that are used to detect the presence of a nucleic acids encoding ATX, or used to detect variations in a nucleic acid sequence encoding ATX, including polymorphisms, for
35 example, single nucleotide polymorphisms.

The nucleic acids of the invention can contain heterologous sequences that are not part of the ATX-encoding sequences in nature. The heterologous nucleic acid sequence can be separated from the ATX-coding sequence by an encoded cleavage site that will permit removal of non-ATX polypeptide sequences from the expressed fusion protein. Heterologous nucleic acid sequences can include sequences encoding epitopes, such as poly-histidine sequences, FLAG tags, glutathione-S-transferase, thioredoxin, and maltose binding protein domains, that facilitate purification of the fusion protein. In addition heterologous nucleic acids can encode domains, such as leucine zipper motifs, that promote multimer formation between the fusion protein and itself or other proteins or immunoglobulins or fragments thereof that can enhance circulatory half-life of the encoded protein.

The nucleic acid molecules of the invention also include DNA sequences encoding ATX species that hybridize under highly or moderately stringent conditions to the non-coding strand, or complement, of the nucleic acid in SEQ ID NO: 1. ATX-encoding nucleic acids of the invention include a) the nucleic acid sequence set out in SEQ ID NO: 1; b) nucleic acids encoding a polypeptide encoded by the nucleic acid of (a), and c) nucleic acids that hybridize to the complement of the nucleic acids of (a) or (b) under moderately or highly stringent conditions. Exemplary high stringency conditions include a final wash in 0.2 X SSC/0.1% SDS at 65°C to 75°C, and exemplary moderate stringency conditions include a final wash at 2 X to 3 X SSC/0.1% SDS at 65°C to 75°C. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as

described in Ausubel, et al. (Eds.), Protocols in Molecular Biology, John Wiley & Sons (1994). Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe.

The invention also provides a vector containing the isolated ATX nucleic acid molecules described above. For example, the invention provides a vector containing an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1.

Vectors include autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors. The invention includes vectors where ATX-encoding nucleic acids are operatively linked to an endogenous or exogenous promoter, enhancer, or operator sequence and a transcription terminator sequence. Promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. It is understood in the art that the choice of host cell is relevant to selection of an appropriate regulatory sequence. Vectors used in the invention can also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct. Vectors can also include sequences that facilitate homologous recombination in a host cell.

Suitable vectors for expression in prokaryotic or eukaryotic cells are well known to those skilled in the art (see, for example, Ausubel et al., supra, 1999). Vectors useful for expression in eukaryotic cells can

include, for example, regulatory elements including the SV40 early promoter, the cytomegalovirus (CMV) promoter, the mouse mammary tumor virus (MMTV) steroid-inducible promoter, Moloney murine leukemia virus (MMLV) promoter, and the like. A vector can include, for example, viral vectors such as a bacteriophage, a baculovirus or a retrovirus; cosmids or plasmids; and, particularly for cloning large nucleic acid molecules, bacterial artificial chromosome vectors (BACs) and yeast artificial chromosome vectors (YACs). Such vectors are commercially available, and their uses are well known in the art. One skilled in the art will know or can readily determine an appropriate promoter for expression in a particular host cell. For example, as disclosed herein, the long form of ATX can be sub-cloned into pcDNA 3.1 with an HA tag and transfected using Fugene 6 into human embryonic kidney 293T cells (Example 2 and Example 5).

Vectors useful for expression of an ATX polypeptide can contain a regulatory element that provides tissue specific or inducible expression of an operatively linked nucleic acid. Such inducible systems, include, for example, tetracycline inducible system (Gossen & Bizard, Proc. Natl. Acad. Sci. USA, 89:5547-5551 (1992); Gossen et al., Science, 268:1766-1769 (1995); Clontech, Palo Alto, CA)); metallothionein promoter induced by heavy metals; insect steroid hormone responsive to ecdysone or related steroids such as muristerone (No et al., Proc. Natl. Acad. Sci. USA, 93:3346-3351 (1996); Yao et al., Nature, 366:476-479 (1993); Invitrogen, Carlsbad, CA); mouse mammary tumor virus (MMTV) induced by steroids such as glucocorticoid and estrogen (Lee et al., Nature, 294:228-232 (1981); and heat shock promoters inducible by temperature changes.

In addition, viral vectors such as retroviral, adenovirus, adeno-associated virus, lentivirus, and herpesvirus vectors can be used to express ATX polypeptides into a cell. Viral based systems provide the advantage of being able to introduce relatively high levels of a heterologous nucleic acid into a variety of cells. Additionally, such viruses can introduce heterologous DNA into nondividing cells. Viral vectors include, for example, Herpes simplex virus vectors (U.S. Patent No. 5,501,979), Vaccinia virus vectors (U.S. Patent No. 5,506,138), Cytomegalovirus vectors (U.S. Patent No. 5,561,063), Modified Moloney murine leukemia virus vectors (U.S. Patent No. 5,693,508), adenovirus vectors (U.S. Patent Nos. 5,700,470 and 5,731,172), adeno-associated virus vectors (U.S. Patent No. 5,604,090), constitutive and regulatable retrovirus vectors (U.S. Patent Nos. 4,405,712; 4,650,764 and 5,739,018, respectively), papilloma virus vectors (U.S. Patent Nos. 5,674,703 and 5,719,054), and the like.

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The invention further provides a host cell containing an ATX-encoding vector as described above. For example, the invention provides a host cell that contains a vector which contains an isolated nucleic acid molecule having substantially the same nucleotide sequence as SEQ ID NO:1. Host cells include prokaryotic and eukaryotic cells. Nucleic acids of the invention can be introduced into the host cell as part of a circular plasmid, or as linear DNA having an isolated protein coding region or a viral vector. Methods for introducing DNA into the host cell are well known in the art and include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, protoplasts, and other transformed cells. Detailed procedures for these methods

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can be found in Sambrook et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1989) and the references cited therein). Expression systems of the invention include bacterial, yeast,
5 fungal, plant, insect, invertebrate, and mammalian cells systems.

Useful mammalian expression vectors and methods of introducing such vectors into mammalian cells either
10 *ex vivo* or *in vivo*, for expression of the encoded polypeptide, are well known in the art. For example, a plasmid expression vector can be introduced into a cell by calcium-phosphate mediated transfection, DEAE-Dextran-mediated transfection, lipofection,
15 polybrene- or polylysine-mediated transfection, electroporation, or by conjugation to an antibody, gramacidin S, artificial viral envelopes or other intracellular carriers. A viral expression vector can be introduced into a cell in an expressible form by
20 infection or transduction, for example, or by encapsulation in a liposome.

The invention also provides a method of producing an ATX polypeptide by a) growing the host cell
25 described above under conditions appropriate for expression of the ATX polypeptide, and b) isolating the ATX polypeptide from the host cell or host cell growth medium. This method can be used to produce ATX polypeptide, for example, as a source of immunogen for
30 the development of antibodies specifically reactive with ATX.

ATX polypeptide isolated from the cells or from the medium in which the cells are grown by purification

methods known in the art, for example, conventional chromatographic methods including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high pressure liquid chromatography (HPLC), reverse phase HPLC, and the like. Still other methods of purification include those wherein the desired protein is expressed and purified as a fusion protein having a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. The purified protein can be cleaved to yield the desired protein, or be left as an intact fusion protein.

The DNA sequence information provided by the present invention also makes possible the development through, for example, homologous recombination or "knock-out" strategies of animals that fail to express functional ATX or that express a variant of ATX (Capecchi, Science 244:1288-1292 (1989)). Such animals are useful as models for studying the *in vivo* activities of ATX and modulators of ATX.

The invention provides an isolated polypeptide containing substantially the same amino acid sequence as SEQ ID NO:2. For example, the invention provides a polypeptide containing an amino acid sequence as referenced in SEQ ID NO:2. The sequence shown in SEQ ID NO:2 corresponds to the "long form" of ATX (Figure 1A).

As described further above, an isolated ATX polypeptide includes conservative and non-conservative amino acid changes to the sequence shown in SEQ ID NO:2. In addition, an isolated ATX polypeptide includes species homologs and fragments of ATX. For example, the

invention provides an isolated ATX polypeptide fragment as referenced in SEQ ID NO:6. Alternatively, the invention provides ATX polypeptide fragments other than the fragment as referenced in SEQ ID NO:6. For example, 5 the invention provides ATX polypeptide fragments that contain carboxyl terminal deletions of a full length ATX polypeptide. Furthermore, an ATX polypeptide can contain polypeptide modifications or heterologous sequences such as an epitope tag. Polypeptides of the invention can be 10 isolated from natural cell sources, chemically synthesized, or produced by recombinant procedures involving the host cells of the invention.

The invention provides an antibody, or antigen 15 binding fragment thereof, which specifically binds to an ATX polypeptide containing an amino acid sequence as referenced in SEQ ID NO:2. Antibodies include, for example, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional or 20 bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR or antigen-binding sequences, which specifically bind to a polypeptide of the invention. 25 Antibody fragments, including Fab, Fab', F(ab')₂, and Fv, are also provided by the invention. Screening assays to determine binding specificity or exclusivity of an antibody of the invention are well known in the art (see Harlow et al. (Eds), Antibodies A Laboratory Manual; Cold 30 Spring Harbor Laboratory; Cold Spring Harbor, N.Y. (1988)).

Antibodies that recognize and bind fragments of the ATX polypeptides of the invention are also 35 contemplated, provided that the antibodies specifically

bind ATX polypeptides. As with antibodies that are specific for full length ATX polypeptides, antibodies of the invention that recognize ATX fragments are those which can distinguish ATX polypeptides from other PIKK polypeptides despite inherent sequence identity,
5 homology, or similarity found in the family of proteins.

Antibodies of the invention can be produced using any method well known in the art, using any
10 polypeptide, or immunogenic fragment thereof, of the invention. Immunogenic polypeptides can be isolated from natural sources, from recombinant host cells, or can be chemically synthesized. For example, as disclosed herein, antibodies specifically reactive with ATX were
15 generated using glutathione S-transferase (GST) fusion proteins containing ATX amino acids 2281-2339 (anti-ATX-Ab-1) or amino acids 1691-1790 (anti-ATX-Ab-2) (Example 2). Polypeptide of the invention can also be conjugated to a hapten such as keyhole limpet hemocyanin
20 (KLH) in order to increase immunogenicity. Methods for synthesizing such peptides are known in the art, for example, as in R. P. Merrifield, J. Amer. Chem. Soc. 85: 2149-2154 (1963); J. L. Krstenansky, et al., FEBS Lett. 211:10 (1987). Antibodies to a polypeptide of the
25 invention can also be prepared through immunization using a nucleic acid of the invention, as described in Fan et al., Nat. Biotech. 17:870-872 (1999). DNA encoding a polypeptide can be used to generate antibodies against the encoded polypeptide following topical administration
30 of naked plasmid DNA or following injection, for example, intramuscular injection, of the DNA.

Non-human antibodies can be humanized by any methods known in the art. In one method, the non-human

CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity. Antibodies of the invention further include plastic antibodies or molecularly imprinted polymers (MIPs) (Haupt and Mosbach, TIBTech 16:468-475 (1998)). Antibodies of this type can be useful in immunoaffinity separation, chromatography, solid phase extraction, immunoassays, for use as immunosensors, and for screening chemical or biological libraries. Advantages of antibodies of this type are that no animal immunization is required, the antibodies are relatively inexpensive to produce, they are resistant to organic solvents, and they are reusable over long period of time.

The invention provides a method for detecting ATX polypeptide in a sample by contacting the sample with an ATX antibody under conditions that allow specific binding of the antibody to the polypeptide and detecting the bound antibody. Antibodies of the invention can also include one or more labels that permit detection of the antibody and antibody binding. Labels can include, for example, radioactivity, fluorescence (or chemiluminescence), one of a high affinity binding pair (such as biotin/avidin), enzymes, or combinations of one or more of these labels. Antibodies of the invention are also useful, for example, for therapeutic purposes (by modulating activity of ATX), diagnostic purposes to detect or quantitate ATX, as well as purification of ATX. Kits containing an antibody or antibodies of the invention are also provided.

The DNA and amino acid sequence information provided by the present invention also makes possible the systematic analysis of the structure and function of ATX. DNA and amino acid sequence information for ATX also
5 permits identification of compounds with which an ATX polypeptide or nucleic acid will interact. Methods to identify compounds that bind to ATX include solution assays, *in vitro* assays where ATX polypeptides are immobilized, and cell based assays. Identification of
10 compounds that bind ATX polypeptides provides potential targets for therapeutic or prophylactic intervention in pathologies associated with ATX biological activity.

The invention provides a method for identifying
15 a compound that specifically binds to an ATX polypeptide of the invention, by a) contacting the ATX polypeptide with a compound, and b) determining specific binding of the compound to said ATX polypeptide. As described further above, the term compound includes macromolecules
20 of natural or synthetic origin including, for example, a polypeptide, peptidomimetic, non-peptidyl compound, carbohydrate, lipid, and antibody or antibody fragment, a small organic or inorganic molecule, or a nucleic acid including an aptamer.

25 Identification of compounds that bind the ATX polypeptide can be achieved by isolating the ATX polypeptide/binding complex, and separating the ATX polypeptide from the binding compound. An additional
30 step of characterizing the physical, biological, or biochemical properties of the binding compound can also be performed. In one embodiment, the ATX polypeptide/binding complex can be isolated using a antibody immunospecific for either the ATX polypeptide or
35 the candidate binding compound. In another embodiment,

the complex can be isolated using a second binding compound that interacts with either the ATX polypeptide or the candidate binding compound. In still another embodiment, either the polypeptide ATX or the candidate binding compound comprises a label or tag that facilitates its isolation, and methods of the invention to identify binding compounds include a step of isolating the ATX polypeptide/binding complex through interaction with the label or tag. An exemplary tag of this type is a poly-histidine sequence, generally around six histidine residues, that permits isolation of a compound so labeled using nickel chelation. Other labels and tags, such as the FLAG tag, thioredoxin, and GST, each of which is well known in the art.

15 An *in vitro* assay can be performed where the ATX polypeptide can be immobilized and then contacted with a candidate binding compound. In an alternative embodiment, the candidate binding compound can be immobilized and binding of the ATX polypeptide is detected. Immobilization can be accomplished using any of the methods well known in the art, including covalent bonding to a support, a bead, or a chromatographic resin, as well as non-covalent, high affinity interaction such as antibody binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a biotin or streptavidin moiety. Detection of binding can be accomplished, for example, (i) using a radioactive label on the compound that is not immobilized, (ii) using of a fluorescent label on the non-immobilized compound, (iii) using an antibody immunospecific for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known in the art.

A cell based assay that can be used in the method of the invention for detecting an ATX binding compound is a yeast or mammalian two-hybrid assay (Fields and Song, Nature 340:245-246 (1989); Fields, Methods: A Companion to Methods in Enzymology 5:116-124 (1993); U.S. Pat. No. 5,283,173 issued Feb. 1, 1994 to Fields, et al.). Modifications and variations on the two-hybrid assay have previously been described (Colas and Brent, TIBTECH 16:355-363 (1998)).

The invention also provides a method for identifying an ATX-modulatory compound by measuring the level of an ATX polypeptide in the presence of a test compound, where a difference in the level of the ATX polypeptide in the presence of the test compound compared to in the absence of the test compound indicating that the test compound is an ATX-modulatory compound. In addition, the invention provides a method for identifying an ATX-modulatory compound by measuring the level of an ATX polypeptide in the presence of a test compound, where a difference in the level of the ATX polypeptide in the presence of the test compound compared to in the absence of the test compound indicating that the test compound is an ATX-modulatory compound, and where the ATX-modulatory compound is not caffeine or wortmannin. The ATX-modulatory compound can decrease or increase the level of ATX polypeptide.

Agents that modulate, for example, increase, decrease, or block the level of ATX can be identified by incubating a test compound with an ATX polypeptide or nucleic acid and determining the effect of the test compound on ATX activity or expression. The level of ATX can include the expression level of ATX or an activity level of ATX. The selectivity, or specificity, of an

ATX-modulatory compound can be evaluated by comparing its effects on ATX or an ATX-encoding nucleic acids to its effect on other polypeptides or compounds. Cell based methods, such as two-hybrid assays to identify DNAs
5 encoding binding compounds and split hybrid assays to identify inhibitors of ATX polypeptide interaction with a known binding polypeptide, as well as *in vitro* methods, including assays where an ATX polypeptide, ATX-encoding nucleic acid, or a binding compound are immobilized, and
10 solution assays are included in this method of the invention.

As understood by those of skill in the art, assay methods for identifying compounds that modulate an
15 activity generally require comparison to a "control." One type of a control is a reaction or cell that is treated substantially the same as the test reaction or cell exposed to the compound, with the distinction that the control reaction or cell is not exposed to the
20 compound.

As disclosed herein, the compounds wortmannin and caffeine can modulate (inhibit) the level of ATX (Example 3 and Example 7). Wortmannin is known to
25 inhibit ATM kinase and is an irreversible inhibitor of PIKKs. Caffeine is a known inhibitor of the G2 cell cycle checkpoint. As disclosed herein, caffeine reversed the accumulation of G2/M phase cells induced by ATX anti-sense treatment, indicating that ATX deficiency can
30 trigger the activation of a caffeine-sensitive G2 checkpoint (Example 7).

The invention provides a method for identifying an ATX-modulatory compound where the level of ATX
35 polypeptide is measured by determining the kinase

activity of the ATX polypeptide. The kinase activity of ATX can be measured using methods well known in the art such as kinase assays and immune complex kinase assays as performed herein in Example 3. These assays contain ATX,
5 a substrate, and a suitable buffer including [g-32 P]ATP and Mn²⁺. Phosphorylated substrates can also be detected using phospho-specific antibodies.

In addition, the invention provides a method
10 for identifying an ATX-modulatory compound where the level of ATX polypeptide is measured by determining the phosphorylation of a p53 polypeptide or fragment. For example, a GST fusion protein containing the first 70 amino acids of p53 (GST-p53₁₋₇₀) can be used as a substrate
15 to measure the level of ATX polypeptide by its kinase activity (Example 3). In addition to p53, the phosphorylation of hUpf1, a helicase, can be used to measure the level of ATX polypeptide (Example 3).

20 The invention also provides a method for identifying an ATX-modulatory compound where the level of ATX polypeptide is measured by determining the level of p53 polypeptide accumulation. As shown herein, a decrease in ATX polypeptide, such as results from the use
25 of an anti-sense oligonucleotide, leads to a reduction in p53 polypeptide accumulation (Example 6). Thus, the level of p53 can be used as a measure of ATX polypeptide level.

30 The invention further provides a method for identifying an ATX-modulatory compound where the level of ATX polypeptide is measured by determining the level of non-sense mediated messenger RNA (mRNA) decay (NMD). NMD is a surveillance mechanism within cells whereby
35 imperfect mRNAs that contain premature translation

termination codons are preferentially degraded. As disclosed herein, treatment of cells with an ATX anti-sense oligonucleotide, which reduced endogenous ATX expression, demonstrated that ATX expression is required for maximal NMD activity (Example 9). The level of NMD is correlated to the level of ATX in the cell and so the level of NMD can be used as a measure of ATX polypeptide level.

ATX-modulatory compounds can be identified that decrease or increase the level of ATX polypeptide or nucleic acid. A decrease in the level of ATX can be a partial reduction or a total blockage of the level of ATX, and an increase in the level of ATX can be a partial increase or an induction of the level of ATX from a previously undetectable level. For example, an ATX-modulatory compound can increase the level of NMD activity in a cell. It can be desirable to increase the level of NMD activity in a cell in order to protect the cell from deleterious gain-of-function mutations caused by truncated polypeptides resulting from the translation of imperfect mRNAs that contain premature translation termination. Alternatively, an ATX-modulatory compound can decrease the level of NMD activity in a cell. It can be desirable to decrease the level of NMD activity in a cell in some cases where the truncated polypeptide does not have a deleterious effect but instead retains some activity that can compensate for the normal gene function.

ATX-modulatory compounds can include, for example, antibodies and other proteins or peptides which specifically bind to an ATX polypeptide or an ATX-encoding nucleic acid, oligonucleotides which bind to an ATX polypeptide or an ATX gene sequence, and other

non-peptide compounds, for example, isolated or synthetic organic and inorganic molecules, which specifically react with an ATX polypeptide or underlying nucleic acid.

ATX-modulatory compounds of the invention can interact specifically or exclusively to an ATX polypeptide or ATX-encoding nucleic acid, however, modulators that interact with an ATX polypeptide or an ATX-encoding nucleic acid with higher affinity or avidity compared to other compounds are also included in the invention.

Mutant ATX polypeptides which affect the enzymatic activity or cellular localization of the wild-type ATX polypeptides are also contemplated by the invention. Targets for the development of ATX-modulatory compounds can include, for example: (1) regions of an ATX polypeptide which contact other proteins, (2) regions that localize an ATX polypeptide within a cell, (3) regions of an ATX polypeptide which bind substrate, (4) allosteric regulatory binding site(s) of an ATX polypeptide, (5) phosphorylation site(s) of an ATX polypeptide as well as other regions of the protein where covalent modification regulates biological activity and (6) regions of an ATX polypeptide which are involved in multimerization of subunits. Still other ATX-modulatory compounds include those that recognize specific ATX-encoding and regulatory nucleic acid sequences.

ATX-modulatory compounds that modulate the level of ATX can be therapeutically useful in treatment of diseases and physiological conditions in which ATX is known or suspected to be involved.

30

Methods of the invention to identify ATX-modulatory compounds include variations on any of the methods described above to identify ATX binding compounds, the variations including techniques where a binding compound has been identified and the binding

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assay is carried out in the presence and absence of a candidate ATX-modulatory compound. A modulatory compound is identified in those instances where the level of binding between an ATX polypeptide and a binding compound changes in the presence of the candidate modulatory compound compared to the level of binding in the absence of the candidate modulatory compound. An ATX-modulatory compound that increases binding between an ATX polypeptide and the binding compound is described as an enhancer or activator, and a modulatory compound that decreases binding between the ATX polypeptide and the binding compound is described as an inhibitor. *In vitro* methods of the invention are amenable to high throughput assays as described below.

In addition to the assays described above which can be modified to identify binding compounds, other methods are contemplated to identify modulatory compounds. In one embodiment, methods of the invention can include use of the split hybrid assay as generally described in WO98/13502 and variations on this method as described in WO95/20652.

The methods of the invention can also utilize high throughput screening (HTS) assays to identify compounds that interact with or inhibit biological activity of an ATX polypeptide. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems include melanophore assays, yeast-based assay systems, and mammalian cell expression systems (Jayawickreme and Kost, Curr. Opin. Biotechnol. 8:629-634 (1997)). Automated (robotic) and miniaturized HTS assays are also embraced (Houston and Banks, Curr. Opin. Biotechnol. 8:734-740 (1997)). HTS assays are designed to identify "hits" or "lead

compounds" having the desired property, from which modifications can be designed to improve the desired property. Chemical modification of the "hit" or "lead compound" is often based on an identifiable
5 structure/activity relationship (SAR) between the "hit" and the ATX polypeptide.

There are a number of different libraries used for the identification of small molecule modulators,
10 including, (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

Chemical libraries consist of structural
15 analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening. Natural product libraries are collections from microorganisms, animals, plants, or marine organisms which are used to create mixtures for screening by, for
20 example, (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) variants thereof.

25 Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds as a mixture. They can be prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Libraries that can be utilized by the invention
30 include peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries
35 created therefrom, see Myers, Curr. Opin. Biotechnol.

8:701-707 (1997). Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to modulate activity.

5

Anti-sense oligonucleotides which recognize and hybridize to nucleic acid encoding ATX can also be utilized by the methods of the invention. Full length and fragment anti-sense oligonucleotides are provided.

10 One skilled in the art of will appreciate that fragment anti-sense molecules of the invention include (i) those which specifically or exclusively recognize and hybridize to ATX-encoding RNA (as determined by sequence comparison of DNA encoding ATX to DNA encoding other molecules) as well as (ii) those which recognize and hybridize to RNA
15 encoding variants of the ATX family of proteins.

Antisense oligonucleotides that hybridize to RNA encoding other members of the PIKK family of proteins are also identifiable through sequence comparison to identify
20 characteristic, or signature, sequences for the family of molecules. Identification of sequences unique to ATX-encoding nucleic acids, as well as sequences common to the family of PIKK-encoding nucleic acids, can be deduced through use of any publicly available sequence
25 database, or through use of commercially available sequence comparison programs. After identification of the desired sequences, isolation through restriction digestion or amplification using any of the various polymerase chain reaction techniques well known in the
30 art can be performed. Anti-sense oligonucleotides can be used for regulating expression of ATX by those cells expressing ATX mRNA. Antisense molecules are generally from about 5 to about 100 nucleotide in length, and preferably are about 10 to 20 nucleotides in length.

35 Antisense nucleic acids capable of specifically binding

to ATX expression control sequences or ATX RNA are introduced into cells, for example, by a viral vector or colloidal dispersion system such as a liposome.

5 The anti-sense nucleic acid binds to the ATX-encoding target nucleotide sequence in the cell and prevents transcription or translation of the target sequence. Phosphorothioate and methylphosphonate anti-sense oligonucleotides are specifically contemplated
10 for therapeutic use by the invention. The anti-sense oligonucleotides may be further modified by poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' end.

15 The invention also provides methods to modulate ATX expression through the use of RNA interference (RNAi) (Brummelkamp et al., Science 296:550-553 (2002); Elbashir et al., Nature 411:494-498 (2002)). RNAi is a process of sequence-specific gene silencing by post-transcriptional
20 RNA degradation, which is initiated by double-stranded RNA (dsRNA) homologous in sequence to the silenced gene. A double-stranded RNA (dsRNA) that is used for RNAi is referred to herein as an "interfering RNA." For example, a suitable dsRNA for RNAi can contain sense and antisense
25 strands of about 21 contiguous nucleotides corresponding to the gene to be targeted that form 19 RNA base pairs, leaving overhangs of two nucleotides at each 3' end (Elbashir et al., *supra*; Bass, Nature 411:428-429 (2001); Zamore, Nat. Struct. Biol. 8:746-750 (2001)). dsRNAs of
30 about 25-30 nucleotides have also been used successfully for RNAi (Karabinos et al., Proc. Natl. Acad. Sci. 98:7863-7868 (2001)). dsRNA can be synthesized *in vitro* and introduced into a cell by methods known in the art. By using RNAi methods, the targeted RNA is degraded, and

translation of the target polypeptide is decreased or abolished.

5 The invention further provides methods to modulate ATX expression through the use of ribozymes (Gibson and Shillito, Mol. Biotech. 7:125-137 (1997)). Ribozyme technology can be utilized to inhibit translation of ATX mRNA in a sequence specific manner through (i) the hybridization of a complementary RNA to a target mRNA and (ii) cleavage of the hybridized mRNA through nuclease activity inherent to the complementary strand. Ribozymes can be identified by empirical methods or be specifically designed based on accessible sites on the target mRNA (Bramlage, et al., Trends in Biotech 10 16:434-438 (1998)). Delivery of ribozymes to target cells can be accomplished using either exogenous or endogenous delivery techniques well known in the art. Exogenous delivery methods can include use of targeting liposomes or direct local injection. Endogenous methods include use of viral vectors and non-viral plasmids. Ribozymes can be ATX-modulatory compounds and specifically modulate expression of ATX when designed to be complementary to regions unique to a nucleic acid encoding ATX. Specifically modulate means that ribozymes of the invention exclusively recognize a nucleic acid 25 encoding ATX.

The invention further provides methods to modulate transcription of ATX through use of 30 oligonucleotide-directed triple helix formation (Lavrovsky, et al., Biochem. Mol. Med. 62:11-22 (1997)). Triple helix formation is accomplished using sequence specific oligonucleotides which hybridize to double stranded DNA in the major groove as defined in the

Watson-Crick model. Hybridization of a sequence specific oligonucleotide can thereafter modulate activity of DNA-binding proteins, including, for example, transcription factors and polymerases. Target sequences for hybridization include promoter and enhancer regions to permit transcriptional regulation of ATX expression. In addition to use of oligonucleotides, triple helix formation techniques of the invention also include use of peptide nucleic acids as described in Corey, TIBTECH 15:224-229 (1997). Oligonucleotides which are capable of triple helix formation are also useful for site-specific covalent modification of target DNA sequences. Oligonucleotides useful for covalent modification can be coupled to various DNA damaging agents as described in Lavrovsky, et al. (*supra*).

Mutations in the ATX gene can result in loss of normal function of the ATX gene product and underlie ATX-related human disease states. The invention therefore provides gene therapy methods to restore ATX activity in treating those disease states described herein. Delivery of a functional ATX gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, for example, viral vectors such as adenovirus, adeno-associated virus, or a retrovirus, or *ex vivo* by use of physical DNA transfer methods such as liposomes or chemical treatments (Anderson, Nature, supplement to vol. 392, no. 6679, pp.25-20 (1998)). Alternatively, in some human disease states, preventing the expression of, or inhibiting the activity of, ATX can be useful in treating the disease states. In this case, anti-sense therapy or gene therapy, for example, where a dominant negative ATX mutant is introduced into a target cell type, can be applied to negatively regulate the expression of ATX.

The invention provides a method for modulating cell survival by introducing an ATX-modulatory compound identified by the methods described above into a cell in an amount effective to modulate survival of the cell.

5 For example, the ATX-modulatory compound can decrease or increase cell survival.

A level of cell death or cell survival can be measured by any of a variety of methods known to one skilled in the art. For example, trypan blue staining
10 can be used to measure the level of cell death in a cell. In addition, clonogenic assays, as described herein, can be used (Example 5). Other staining methods, for example, propidium iodide and Alomar Blue, also can be
15 used to measure cell death. The stained cells can be visualized in any way that is convenient, for example, by microscopy or flow cytometry (FACS). In addition, cell viability and cell proliferation assays such as the lactose dehydrogenase (LDH) assay and the MTT
20 (3-(4,5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assay are commercially available and can be used to measure cell viability. In addition, the uptake of 3H thymidine can be used to access the viability of cells.

25 The invention further provides a method for modulating cell survival by introducing an ATX-modulatory compound into a cell where the cell is exposed to a stressor agent. As described further above, a stressor agent is any agent that can induce a stress response
30 pathway within a cell. A stressor agent can include, for example, UV light, ionizing radiation, reactive oxygen intermediates, or a chemical agent such as a cytotoxic or chemotherapeutic agent. In addition, environmental conditions such as excessive heat can induce a stress
35 response pathway within a cell resulting in, for example,

the induction of heat shock proteins. Stress response pathways include DNA repair pathways, non-sense mediated mRNA decay (NMD), heat shock pathways, the induction of apoptosis, activation of the NFkB transcription factor, 5 activation of the stress-activated MAP kinase pathways including, for example, JNK and p38 pathways, and activation of ubiquitin-dependent proteolysis.

10 An example of an ATX-modulatory compound of the invention is an antisense oligonucleotide. The invention provides a method for decreasing cell survival by introducing an antisense oligonucleotide, such as SEQ ID NO: 11 into a cell in an amount effective to decrease survival of the cell.

15 Association of ATX with cell cycle progression makes compositions of the invention, including for example an ATX polypeptide, an inhibitor thereof, an antibody, or other modulator of ATX expression or 20 biological activity, useful for treating a number of conditions. For example, the invention provides a method for treating a condition characterized by excessive cell survival or cell growth by administering to a patient having such a condition an effective amount of an 25 ATX-modulatory compound where the effective amount of the compound increases cell death. For example, an ATX-modulatory compound can be given to a patient with a neoplastic condition.

30 An ATX-modulatory compound that decreases the level of ATX can enhance the radiosensitivity or chemosensitivity of neoplastic cells. Therefore, it is contemplated that an ATX-modulatory compound can be given alone or in combination with another agent such as a 35 cytotoxic or chemotherapeutic agent. Several cytotoxic

agents, such as radiation, and chemotherapeutic agents, such as cis-platin, are well known in the art. An appropriate agent can be chosen based on several factors, such as the particular type of neoplastic condition at
5 issue or the ability of the patient to tolerate the agent. For example, focused radiation therapy, including brachytherapy, can be used in conjunction with an ATX inhibitory compound in order to induce tumor cell death while minimizing cytotoxic effects on normal tissue.

10

A "neoplastic condition," refers to a condition associated with hyperproliferation of cells and includes benign and malignant expanding lesions of proliferating cells. Neoplastic conditions include benign and
15 malignant hyperproliferative disorders. A benign neoplasm grows in an expansile manner, displacing or compressing surrounding tissues rather than invading them. A malignant neoplasm refers to a large group of diseases characterized by uncontrolled growth and spread
20 of abnormal cells. Cancer, for example, is a malignant neoplastic condition that encompasses many sub-conditions that are characterized by insufficient death of abnormal cells. Tumors of the colon, prostate, lung, cervix, stomach, breast and skin are examples of neoplastic
25 conditions.

Aberrant ATX activity can be associated with various forms of cancer in, for example, adult and pediatric oncology, including growth of solid
30 tumors/malignancies, myxiod and round cell carcinoma, locally advanced tumors, metastatic cancer, human soft tissue sarcomas, cancer metastases, including lymphatic metastases, squamous cell carcinoma of the head and neck, esophageal squamous cell carcinoma, oral carcinoma, blood

cell malignancies, including multiple myeloma, leukemias, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancer, including small cell carcinoma, non-small cell cancers, breast cancer, including small
5 cell carcinoma and ductal carcinoma, gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, polyps associated with colorectal neoplasia, pancreatic cancer, liver cancer, urological cancers, including bladder cancer, including primary
10 superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscle-invasive bladder cancer, prostate cancer, malignancies of the female genital tract, including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma,
15 uterine endometrial cancers, and solid tumors in the ovarian follicle, kidney cancer, including renal cell carcinoma, brain cancer, including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous
20 system, bone cancers, including osteomas, skin cancers, including malignant melanoma, tumor progression of human skin keratinocytes, and squamous cell cancer, hemangiopericytoma, and Kaposi's sarcoma.

25 Aberrant ATX activity also can be associated with other conditions which include aberrant apoptotic mechanisms, including abnormal caspase activity; aberrant enzyme activity associated with cell cycle progression, including for example cyclins A, B, D and E; alterations
30 in viral (such as Epstein-Barr virus, papillomavirus) replication in latently infected cells; chromosome structure abnormalities, including genomic stability in general, unrepaired chromosome damage, telomere erosion (and telomerase activity), breakage syndromes including
35 for example, Sjogren's syndrome and Nijmegen breakage

syndrome; embryonic stem cell lethality; abnormal embryonic development; sensitivity to ionizing radiation; acute immune complex alveolitis; and Fanconi anemia. ATX-modulatory compounds can be used alone or in
5 combination with another agent in the treatment of these conditions.

The invention also provides a method for treating a condition characterized by excessive cell
10 death by administering to a patient having such a condition an effective amount of an ATX-modulatory compound where the effective amount of the compound increases cell survival. For example, an ATX-modulatory compound can be given to a patient with a
15 neurodegenerative condition in order to increase neuronal cell survival. In addition the invention provides a method of prolonging the *in vivo* survival of transplanted cells for the treatment of a disease or pathological condition. Also, for example, a compound that increases
20 the level of ATX can be given to a patient who is exposed to stressors such as UV light in order to protect against genetic mutations.

The effective compounds of the invention
25 described herein can optionally be formulated together with a pharmaceutically acceptable carrier for delivery to a cultured cell or to a subject. Suitable pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous or organic
30 solvents such as physiologically buffered saline, glycols, glycerol, oils or injectable organic esters. A pharmaceutically acceptable carrier can also contain a physiologically acceptable compound that acts, for example, to stabilize or increase the solubility of a
35 pharmaceutical composition. Such a physiologically

acceptable compound can be; for example, a carbohydrate, such as glucose, sucrose or dextrans; an antioxidant, such as ascorbic acid or glutathione; a chelating agent; a low molecular weight polypeptide; or another stabilizer
5 or excipient. Pharmaceutically acceptable carriers, including solvents, stabilizers, solubilizers and preservatives, are described, for example, in Martin, Remington's Pharm. Sci., 15th Ed. (Mack Publ. Co., Easton, 1975).

10

Those skilled in the art can formulate the therapeutic molecules to ensure proper distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure
15 that the effective compounds of the invention cross the BBB, if desired, they can be formulated, for example, in liposomes, or chemically derivatized. For a review of strategies for increasing bioavailability of polypeptide drugs in the brain, and of methods for determining the
20 permeability of polypeptides through the BBB using *in vitro* and *in vivo* assays, see Engleton et al., Peptides 9:1431-1439 (1997). Strategies that have been successfully used to increase the permeability of other neuropeptides through the BBB are particularly
25 contemplated. Modifications to a polypeptide of the invention that can increase its BBB penetration include conjugating the peptide to a lipophilic moiety, such as a lipophilic amino acid or methyl dihydropyridine. Similar modifications to invention polypeptides or
30 peptidomimetics are likewise expected to be advantageous.

Methods of ensuring appropriate distribution *in vivo* can also be provided by rechargeable or biodegradable devices, particularly where gradients of
35 concentrations of drug in a tissue are desired. Various

slow release polymeric devices are known in the art for the controlled delivery of drugs, and include both biodegradable and non-degradable polymers and hydrogels. Those skilled in the art understand that the choice of the pharmaceutical formulation and the appropriate preparation of the composition will depend on the intended use and mode of administration.

The effective compounds of the invention can be administered to a subject by any effective route. Suitable routes for delivering the therapeutic molecules of the invention include topically, intraocularly, intradermally, parenterally, orally, intranasally, intravenously, intramuscularly, intraspinally, intracerebrally and subcutaneously. The present invention also provides compounds containing an acceptable carrier such as any of the standard pharmaceutical carriers, including phosphate buffered saline solution, water and emulsions such as an oil and water emulsion, and various types of wetting agents.

An effective dose of an effective compound of the invention can be determined, for example, by extrapolation from the concentration required in the ATX binding or ATX activity assays described herein; or from the dose required to modulate cell proliferation. An effective dose of an effective compound of the invention for the treatment of a pathology can also be determined from appropriate animal models, such as transgenic mice. Animal models for pathologies such as tumors are well-known in the art. An effective dose for treating this disease is a dose that results in either partial or complete regression of the tumor, reduction in metastasis, reduced discomfort, or prolonged life span. The appropriate dose for treatment of a human subject

with a therapeutic molecule of the invention can be determined by those skilled in the art, and is dependent on the nature and bioactivity of the particular compound, the desired route of administration, the gender, age and health of the individual, the number of doses and duration of treatment, and the particular condition being treated.

It is understood that modifications which do not substantially affect the activity of the various embodiments of this invention are also included within the definition of the invention provided herein. Accordingly, the following examples are intended to illustrate but not limit the present invention.

15

EXAMPLE 1

Molecular Cloning of ATX

This example shows the cloning of ATX nucleic acids. During a BLAST search for mTOR-related proteins, it was noted that an expressed sequence tag (EST) (KIAA0421) contained a 5'-terminus with an open reading frame (ORF) that bore clear homology to a conserved region in the catalytic domains of PIKK family members. To access the full-length cDNA, the EST was used to generate a primer for 5'-RACE with human brain cDNA as the template. The initial 5'-RACE product extended the region of homology with the PIKK catalytic domain. Sequential screens of human brain (Clontech #HL1128a) and Jurkat T cell cDNA libraries (Stratagene #936219), combined with 5'-RACE of brain and Jurkat cDNA, resulted in the isolation of several overlapping DNA fragments that were assembled into approximately 12 kb of contiguous nucleotide sequence. This cDNA contains an ORF of 10,563 nucleotides with an additional 1.8kb of

3'-UTR, and encodes a 3,521 amino acid polypeptide with a deduced molecular mass of 395 kDa. The first nucleotide of the ATG translation initiation codon in exon 6 as has been designated as nucleotide "1", and nucleotides
5 upstream of this ATG are identified in the 3' to 5' direction with negative numbers. The conclusion that this sequence was derived from a single mRNA transcript was confirmed by PCR with primers that were complementary to the extreme 5'-terminus (nucleotides -90 to -67) and
10 3'-terminus (nucleotides 10,553 to 10,570) of the corresponding cDNA. The cloned cDNA sequence is contained in a genomic BAC clone (AC020716), which allowed localization of the gene encoding this putative PIKK family member to human chromosome 16. Based on its
15 functional overlap with ATM, this new PIKK family member was named "ATX".

The collective results of the 5'-RACE and RT-PCR assays of mRNA derived from Jurkat T cell, human
20 brain, and other human cell lines indicated that the ATX locus gives rise to several mRNA transcripts (Figure 1A). One repetitively isolated ATX cDNA clone contains exon 4 spliced directly to exon 6, and yields the 3,521 amino acid polypeptide described above. This mRNA transcript
25 and encoded polypeptide has been designated "long ATX", to distinguish it from a "short ATX" polypeptide (3,031 amino acids) produced as a result of allelic variation in exon 15, which leads to the insertion of 27 nucleotides beginning at nucleotide 1427 (Figure 1A). This sequence
30 alteration causes the insertion of two in-frame stop codons, and use of the next available ATG codon (in exon 16) as the translational start site gives rise to the amino-terminally truncated, short form of ATX. The 5' end of the ATX allele that encodes short ATX is contained
35 within a second genomic BAC clone (AC003007) derived from

human chromosome 16. Yamashita et al. have identified two human cDNA clones, both designated *hSMG-1*, one of which (Figure 1A, second from bottom, SEQ ID NO: 7) was similar to the long ATX cDNA clone (SEQ ID NO:1)

5 (Yamashita et al., Genes and Development 15:2215-2228 (2001)). Exon 5 was not included in our long cDNA clone due to the infrequent appearance of this exon during our 5'-RACE and RT-PCR analyses of human cell line-derived mRNA. Furthermore, the minority of cDNAs that did

10 include the exon 5 sequence frequently contained exon 3, which placed an in-frame stop codon at the 5'-end of this cDNA (Figure 1A). The longest ATX cDNA clone (ORF beginning at exon 2, SEQ ID NO:9) identified by Yamashita et al. (Yamashita et al., supra, 2001) was also isolated

15 in our screening procedure. However, it was repeatedly found that the exon 3-associated stop codon was present in this transcript.

Example 2

20 Expression of endogenous and recombinant ATX

In order to examine the expression of ATX mRNA in various tissues, a multiple tissue Northern blot was hybridized with a 32P-labelled, ATX cDNA probe that

25 spanned exons 38-39 (nucleotides 5,071-5,370). The ATX probe detected a major mRNA species that, based on its electrophoretic mobility, was significantly larger than the 9.5 kb calibration marker, and could reasonably accommodate the predicted ORF (10.5 kb) of long ATX (data

30 not shown). This ATX transcript was widely expressed in human tissues, with the highest levels observed in heart and skeletal muscle. These results are consistent with those obtained in immunoblot analyses with ATX-specific antibodies, which showed that ATX protein was uniformly

35 expressed in hematopoietic, mesenchymal, and epithelial

cell lines (data not shown). Database searches with the ATX amino acid sequence revealed the highest degree of homology to *C. elegans* SMG1, a protein required for NMD in the worm. Both ATX and CeSMG1 contain the PI 3-kinase related catalytic domain, which identifies these proteins as members of the PIKK family (Figure 1B). Outside of the catalytic domain, the regional sequence homology between ATX and other PIKK family members was limited to the FKBP-12•rapamycin binding (FRB, designated NH2 in Figure 1B) domain of mTOR, and to the NH1 and NH2 domains of CeSMG1. The FRB domain mediates the high-affinity interaction between mTOR and the antiproliferative FKBP12•rapamycin complex (Chen et al., Proc. Natl. Acad. Sci. USA, 92:4947-4951 (1995)). However, the FRB-related domain of ATX does not confer any detectable binding affinity for FKBP12•rapamycin (data not shown); hence, it is unlikely that ATX is a relevant target for rapamycin in intact cells. The expression of the short and long forms of ATX were compared after transient transfection of the respective cDNAs into human embryonic kidney 293T cells. The short ATX polypeptide was poorly expressed relative to long ATX (data not shown). However, these results do not exclude the possibility that the shorter form of ATX is expressed and contributes to the overall functions of ATX in mammalian cells.

In order to compare the translation product derived from the long ATX cDNA with the endogenously expressed ATX polypeptide, HEK 293T cells were transfected with HA-tagged expression plasmids encoding either wild-type ATX (HA-ATXWT) or a catalytically inactive ATX mutant (HA-ATXKI). The HA-ATXKI mutant contains an Asp>Ala substitution at a conserved residue (Asp-2195) in the ATX catalytic domain. Similar mutations in the catalytic domains of ATM, ATR, and

DNA-PKCS have been shown to generate kinase-inactive (KI) versions of these PIKK family members (Canman et al., Science, 281:1677-1679 (1998); Cliby et al., EMBO Journal, 17:159-169 (1998); Hunter, *supra*, 1995).

5

For analyses of the endogenous ATX protein, two different rabbit polyclonal antibodies were prepared against GST fusion proteins containing peptide fragments derived from ATX. The first antibody (α -ATX Ab-1) was generated against a GST fusion protein containing amino acids 2281-2339 of ATX, while the second (α -ATX Ab-2) was obtained from immunizations with GST fused to amino acids 1691-1790 of ATX. The α -ATX Ab1 immunoblot analyses of whole cell extracts from non-transfected or HA-ATX-transfected HEK 293T cells revealed a single major immunoreactive band migrating at the predicted molecular mass of ~395 kDa (data not shown). An immunoreactive protein bearing a nearly identical electrophoretic mobility was detected in α -HA immunoprecipitates from transfected 293T cells. These results indicate that the molecular mass of the recombinant protein produced from the long ATX cDNA corresponds closely to that of the endogenous ATX protein. Consistent with the predicted size of ATX, the band recognized by the α -ATX antibodies migrated with a significantly lower electrophoretic mobility than either ATM (molecular mass, 370 kDa) or ATR (molecular mass, 305 kDa).

Methods:

30 *Cloning*

The longer ATX ORF was appended with an amino-terminal hemagglutinin (HA) epitope tag sequence (CYPYDVPDYASL), and was subsequently amplified as two partially overlapping fragments from Jurkat cDNA. The nucleotide at position 4,620 was mutated in each of the two PCR

35

products to create a *Sac*II site that could be utilized to ligate the two ATX fragments, which were inserted into the *Xho*I and *Not*I sites of pcDNA3.1 (Invitrogen) (HA-ATX). The mutation used to generate the *Sac*II did not
5 alter the ATX polypeptide sequence. The expression vector encoding the catalytically inactive ATX mutant (HA-ATXKI) contains an Ala substitution at Asp-2195, which was generated by site-directed mutagenesis with the QuickChange kit (Stratagene). All plasmid constructs were
10 sequenced to insure the fidelity of the PCR and cloning procedures.

Cell lines

U2OS osteosarcoma and human embryonic kidney (HEK) 293T
15 cells were cultured in low-glucose Dulbecco's Modified Eagle's Medium (DMEM), supplemented with 10% fetal bovine serum. The ATM-deficient human fibroblast line, AT4BI, was maintained in DMEM/F-12 medium supplemented with 10% fetal bovine serum. Where indicated, cells were
20 γ -irradiated with a ¹³⁷Cs source or UV irradiated with a UV-B source (λ_{max} , 305 nm).

Antibodies

ATX-specific antibodies were raised by immunizing rabbits
25 (Cocalico Biologicals, Inc.) with the indicated glutathione S-transferase (GST) fusion protein. Anti-ATX Ab-1 was raised against a GST fusion protein containing ATX amino acids 2281-2339, and α -ATX Ab-2 was raised against a GST fusion protein containing ATX amino acids
30 1691-1790. For purification of α -ATX Ab-2, GST-reactive antibodies were first absorbed on GSH-agarose. The flow-through fraction was then affinity purified over Affi-Gel 15 (BIO-RAD) coupled to the GST-ATX1691-1790 fusion protein. The α -PLC- γ 1 antiserum was prepared as
35 described (Secrist et al., J. Biol. Chem., 268: 5886-5893

(1993)). The α -ATM (Ab-3), α -ATR (Ab-1), α -phospho-Ser15-p53, and α -p53 (Ab-6) reagents were obtained from Oncogene Science Research Products. Additional antibodies were obtained from (sources in
5 parentheses): α -HA (clone 12CA5; BabCo), α -FLAG-M2 and α -tubulin (Sigma), α -Cds1/Chk2 (Upstate Biotechnology), and α -GAL4 (clone RK5C1; Santa Cruz Biotechnology).

Two-dimensional PAGE

10 HEK 293 cells were lysed and protein analyzed as described {Pal, 2001 #1360}, except that cellular extracts were incubated for 2 h with α -FLAG-M2 mAb, followed by 2 h with protein G agarose (Sigma) to immunoprecipitate the FLAG-hUpf1 protein. Prior to
15 elution, the immunoprecipitates were washed in lysis buffer as described {Pal et al., Rna 7:5-15 (2001) #1360}.

Immunofluorescence

For immunofluorescence microscopy of endogenous ATX, 6 x
20 104 U2OS cells were plated onto 22-mm² glass coverslips. After 40 h, cells were exposed to 400 J/m² UV-B, then fixed 1, 4 or 8 hrs later in phosphate-buffered saline (PBS) containing 4% paraformaldehyde for 20 min, and incubated in methanol at -20° for 15 min. The coverslips
25 were rehydrated in phosphate-buffered saline (PBS) and incubated overnight at 4° C in blocking solution (PBS containing 3% BSA and 2% goat serum). Coverslips were subsequently overlayed for 1 h with affinity purified α -ATX Ab-2 (1 μ g per ml) in blocking solution at room
30 temperature. Coverslips were washed with PBS, 0.2% Tween-20, and overlayed for 45 min at room temperature with fluorescein isothiocyanate (FITC)-conjugated goat anti-rabbit IgG (Caltag) (1:2000 in blocking solution). Samples were then washed and incubated with 100 μ g per ml
35 RNaseA in PBS for 30 min, followed by 1 μ g per ml

propidium iodide for 5 min. After extensive washing in PBS containing 0.2% Tween-20, coverslips were mounted on slides with an aqueous anti-fade mounting reagent (Vectashield, Vector Laboratories). Immunofluorescence
5 images were generated with a Carl Zeiss LSM410 scanning laser confocal microscope.

Example 3

Characterization of ATX kinase activity

10

With the exception of the TOR proteins, the PIKK family members that bear functional catalytic domains phosphorylate substrates bearing the Ser/Thr-Gln motif (Tibbetts and Abraham, *supra*, 2000). To determine
15 whether the ATX kinase domain displayed a similar phosphorylation site selectivity, HEK 293T cells were transfected with a plasmid vector encoding HA-tagged ATXWT, ATXKI, or, for comparative purposes, HA-ATMWT. Detergent extracts from the transfected cell populations
20 were immunoprecipitated with α -HA antibody, and protein kinase assays were performed in buffer containing Mn^{2+} , [γ - ^{32}P]ATP, and a GST fusion protein containing the first 70 amino acids of p53 (GST-p53₁₋₇₀) as the substrate (Fig 1C). The GST-p53₁₋₇₀ protein was previously identified as
25 a substrate for ATM and ATR in immune complex kinase assays (Tibbetts et al., Genes and Development 13:152-157 (1999)). Interestingly, the specific kinase activity of HA-ATXWT towards GST-p53₁₋₇₀ was significantly higher than that of HA-ATM (Fig 1C, *left panel*). Based on the ratios
30 of ^{32}P incorporation into substrate to levels of HA-tagged protein kinase, it can be estimated that the specific kinase activity of ATXWT was approximately 3.5-fold higher than that of ATMWT. As observed with ATM as the test kinase (Banin et al., Science 281:1674-1677
35 (1998); Canman et al., Science 281:1677-1679 (1998);

Tibbetts et al., *supra*, 1999), phosphorylation of GST-p53₁₋₇₀ by ATXWT was nearly abolished by substitution of the Ser-15 residue in p53 with Ala (Fig 1C, *right panel*). Because Ser-15 resides in the optimal sequence (LSQE) for phosphorylation by ATM (O'Neill et al., J. Biol. Chem. 275:22719-22727 (2000)), this finding indicates that ATX is a Ser/Thr-Gln-directed kinase, with the potential to phosphorylate a set of substrates that overlaps with those modified by ATM. In contrast to the amino-terminal fragment of p53, the PHAS-I/4E-BP1 protein, which is the prototypical substrate for mTOR, was poorly phosphorylated by HA-ATXWT in immune complex kinase assays (data not shown).

The amino acid sequences surrounding the four phosphorylation sites (LSQP, LSQD, LSQD, and LSQY) identified in this study resemble the consensus site for phosphorylation by ATM (O'Neill et al., *supra*, 2000). A GST fusion protein that contained the carboxyl-terminal region of hUpf1 (amino acids 1019-1118), including all four of the ATX phosphorylation sites was constructed. This GST-hUpf11019-1118 protein was tested as a substrate for HA-ATXWT versus HA-ATMWT in immune complex kinase assays. Once again, this substrate was phosphorylated by both ATM and ATX, with the latter protein kinase showing the higher specific catalytic activity under these *in vitro* assay conditions (Figure 1C, *left panel*). Furthermore, the results of repeated assays indicated that GST-p53₁₋₇₀ was more avidly phosphorylated by ATX than was the GST-hUpf11019-1118 substrate.

The protein kinase activities of the mammalian PIKKs characteristically display a strong dependence on Mn²⁺ as a cofactor for the phosphotransferase reaction, and variable sensitivity to inhibition by wortmannin

(Abraham, Genes and Development 15:2177-2196 (2001)). In our studies, the protein kinase activity of ATX was also dependent on the addition of Mn²⁺ to the kinase reaction buffer (data not shown). In addition, pretreatment of the immunoprecipitated HA-ATXWT protein with wortmannin resulted in a concentration-dependent inhibition of GST-p53₁₋₇₀ phosphorylation. The drug concentration required for 50% inhibition (IC₅₀) of ATX activity *in vitro* was between 10 and 100 nM (Figure 1D), which is comparable to the previously published IC₅₀ (80 nM) for wortmannin as an ATM inhibitor (Sarkaria et al., Cancer Res. 58:4375-4382 (1998)). Wortmannin is an irreversible inhibitor of PIKKs (Walker et al., Molecular Cells 6:909-919 (2000)) and can be used to assess the potency of this drug as an ATX inhibitor in intact cells. To this end, U2OS osteosarcoma cells were pretreated for 30 min with the indicated concentrations of wortmannin, followed by the preparation of cellular extracts for immunoprecipitation of endogenous ATX with α -ATX Ab-2. Under these conditions, wortmannin inhibited ATX kinase activity with an IC₅₀ of 1-3 μ M, which is considerably higher than that observed following direct treatment of the immunoprecipitated protein kinase with this drug (Figure 1D). A similarly dramatic decrease in the inhibitory potency of wortmannin was observed with ATM as the target enzyme in intact cells (Sarkaria et al., *supra*, 1998).

Immune complex kinase assays

Native or recombinant ATX proteins were immunoprecipitated from cell extracts as described above, and the immunoprecipitates were washed twice in lysis buffer, once in high-salt buffer (100 mM Tris-HCl, pH 7.4, 500 mM LiCl) and once in kinase buffer (10 mM Hepes, pH 7.4, 50 mM NaCl, 50 mM β -glycerol phosphate). Forty

10 μl kinase buffer (containing 10% glycerol, 1 mM DTT, 10
15 mM MnCl₂, 20 nM microcystin, protease inhibitors, 1 μg of
the indicated substrate, 10 μM ATP, and 10 μCi [γ-³²P]ATP
(6000 Ci/mmole) (NEN)] was added to each sample, and
kinase reactions were performed for 30 min at 30°C.
Reactions were terminated by addition of 40 μl of
4X-SDS-PAGE sample buffer, and heating to 100°C.

Example 4

10 Subcellular localization of ATX

15 The subcellular localization of ATX was
examined by biochemical fractionation of U2OS cells,
followed by immunoprecipitation of crude nuclear and
cytoplasmic fractions with α-ATX Ab-2. Comparable levels
of ATX were found in the nuclear and cytoplasmic extracts
from U2OS cells (data not shown). The integrity of these
subcellular fractions was confirmed by
immunoprecipitation and immunoblotting of parallel
20 samples with antibodies specific for PLCγ1 and ATR, which
are localized to the cytoplasm and nucleus, respectively.
The presence of ATX in both the cytoplasmic and nuclear
compartments was further documented by immunostaining of
U2OS cells with affinity-purified α-ATX Ab-2. Exposure
25 of cells to genotoxic agents triggers the appearance of
DNA damage-induced nuclear foci containing either ATM or
ATR (Andegeko et al., J. Biol. Chem. 276:38334-38230
(2001); Tibbetts et al., Genes and Development
14:2989-3002 (2000)). To determine whether ATX undergoes
30 similar changes in subcellular localization in response
to genotoxic stress, U2OS cells were treated with 400
J/m² UV-B, and stained with α-ATX Ab-2. Exposure to UV
triggered the appearance of ATX-containing nuclear foci.
The ATX-positive foci were evident within 1 h after UV
35 treatment, and continued to accumulate in the cells until

at least 8 h post-treatment, at which time greater than 50% of the cells exhibited multiple ATX-containing foci. In contrast, the formation of ATX foci after treatment of U2OS cells with 20 Gy IR was not detected.

5

In addition, the effect of genotoxic stress on the protein kinase activity of ATX in immune complex assays was determined. Consistent with the results of the immunofluorescence staining experiments, treatment of the cells with IR failed to induce a reproducible increase in the protein kinase activity observed in α -ATX immunoprecipitates (data not shown). On the other hand, UV exposure caused a modest but consistent increase in ATX kinase activity that reached a maximal level at 4 h post-irradiation. Collectively, the results of the nuclear localization and protein kinase activity studies indicated that, like ATM and ATR, ATX participated in cellular responses to DNA damage or other forms of stress induced by UV irradiation.

15
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Methods:

Cell fractionation, immunoprecipitation, and immunoblotting

For subcellular fractionations, U2OS cells were resuspended in cold homogenization buffer (25 mM Hepes, pH 7.4, 250 mM sucrose, 1 mM EGTA, 5 mM MgCl₂, 50 mM NaF, 1mM DTT, plus protease inhibitors) and Dounce homogenized on ice with 40 strokes in a Tefloncoated homogenizer. The nuclei were pelleted at 500 x g, and the supernatant was collected as the crude cytoplasmic fraction. Prior to immunoprecipitation, 150 mM NaCl and 1% (wt/vol) NP-40 (final concentration) were added to the crude cytoplasmic fractions. Nuclear extracts were prepared by suspending the nuclear pellets in extraction buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% NP-40, 1 mM dithiothreitol),

30
35

supplemented with protease inhibitors (10 µg per ml leupeptin, 10 µg per ml aprotinin, 1 µM pepstatin). After 15 min on ice, the samples were centrifuged, and the supernatant was collected for analysis. For immunoprecipitations, cell extracts were prepared by resuspending washed cell pellets in lysis buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% NP-40, 1 mM dithiothreitol) plus protease inhibitors. When samples were prepared for immune complex kinase assays, the lysis buffer was modified to contain 1% Tween-20 detergent in place of NP-40, and additional phosphatase inhibitors (20 mM β-glycerol phosphate and 50 nM microcystin). Samples were incubated on ice for 15 min, and then clarified by centrifugation. HA-tagged recombinant proteins were immunoprecipitated from cell extracts with 4 µg of α-HA antibody. Endogenous ATX protein was immunoprecipitated with 8 µg of α-ATX Ab-2. After separation by SDS-PAGE, the proteins were detected by autoradiography (for kinase reaction products) or by immunoblotting. Proteins immunoblotted with rabbit and mouse antibodies were detected with protein A-horseradish peroxidase (HRP) (Amersham), and sheep anti-mouse IgG-HRP (Amersham), respectively. Immunoreactive proteins were illuminated with Renaissance chemiluminescence system (NEN).

Example 5

Effect of decreased ATX function on cellular sensitivity to UV and IR

In order to gain further insights into the role of ATX in stress responses, U2OS cells were transfected with the kinase-inactive ATXKI mutant, and the UV- and IR-sensitivities of the transfected cells in clonogenic survival assays was examined. Control cell populations were transfected with either empty plasmid (pcDNA3.1) or

with ATXWT-encoding plasmid. At 48 h post-transfection, the cells were treated with various doses of UV-B (Figure 2A) or IR (Figure 2B). The treated cells were then cultured in G418-containing medium in order to select for stably transfected cells. Cellular survival was determined after 10 days in culture by staining emergent colonies with Coomassie blue, followed by colorimetric quantitation of the amount of dye-bound protein present in each sample. Expression of ATXKI, but not ATXWT, reduced the basal survival of otherwise untreated U2OS cells (Figure 2B, *top panel*). These results indicate that endogenous ATX function is required for the maintenance of normal cell viability or growth in culture. Furthermore, expression of ATXKI dramatically increased the sensitivity of U2OS cells to the cytostatic/cytotoxic effects of both UV and IR in these clonogenic survival assays.

To address concerns related to potential non-specific effects of ATXKI expression on cellular functions, an antisense oligonucleotide-based approach to reduce the level of ATX expression in U2OS cells was developed. The cells were mock transfected, or transfected with sense (S) or antisense (AS) oligonucleotides, and then treated for 24 h with various genotoxic agents. The cells were then trypsinized and replated, and clonogenic survival was analyzed after 10 days in culture. The results obtained with AS-treated cells were strikingly similar to those obtained with the ATXKI-expressing cells (Figures 2 A-C). While transfection of U2OS cells with the S oligonucleotide reduced the basal level of colony outgrowth by 25%, treatment with the AS oligonucleotide decreased basal clonogenic activity by 75% (Figure 2C, *right panel*). Hence, the AS-induced decrease in ATX protein expression

was accompanied by a reduction in cell viability or proliferation in the absence of environmental stress. Furthermore, the AS-treated cells were significantly more sensitive to the suppressive effects of IR (Figure 2C, left panel) and UV treatments (data not shown) on clonogenic survival. The reduction in ATX protein caused by AS treatment ranged from 50-90% in over 10 independent trials.

10 **Methods:**

Cell transfections

To prepare recombinant HA-tagged ATX and ATM proteins, HEK 293T cells were plated onto 60-mm dishes (9 x 10⁵ cells per dish), and were transfected with 5 µg pcDNA3.1 (empty vector), HA-ATXWT, HA-ATXKI, or HA-ATMWT plasmid DNAs. Transfections were performed with the Fugene 6 transfection reagent (Roche), according to the manufacturer's instructions. For NMD assays (see Example 9, below), U2OS cells were seeded onto 100 mm dishes (1 x 10⁶ cells per dish). After 20 h, cells were transfected with 1.5 µg of pmCMV-G1 test plasmid, either Norm or 39Ter (Ishigaki et al., 2001); 1.5 µg of phCMV-MUP reference plasmid (Ishigaki et al., Cell 106:607-617 (2001)); and 7 µg of empty plasmid (pcDNA 3.1), plasmids encoding HA-ATMWT, HA-ATMKI, HA-ATXWT or HA-ATXKI. For antisense transfection experiments, U2OS cells were seeded onto 60 mm dishes (1 x10⁵ cells per dish) in complete medium supplemented with penicillin /streptomycin. After 30 h, cells were either mock transfected or transfected with sense (S) or antisense (AS) phosphorothioate oligonucleotides (Genset Oligos, La Jolla, CA). The S oligonucleotide spans ATX nucleotides 210-229 (5'-GAGACAGGAGGGAGCTTGCT-3'), and the AS oligonucleotide is complementary to this sequence (5'-AGCAAGCTCCCTCCTGTCTC-3'). The cells were transfected

with oligonucleotides at final concentrations of 8 µg/ml, with Fugene 6:DNA ratio of 1.6:1. Forty-eight hours after transfection, dishes were exposed to IR, UV-B, or 5-FU, and then harvested for immunoblotting, cell-cycle distribution, or cell survival assays. To examine ATX protein levels in oligonucleotide-treated cells, whole cell extracts were resolved by SDS-PAGE and immunoblotted with α-ATX Ab-1. When oligonucleotide-transfected cells were used for NMD assays, U2OS cells were seeded in culture dishes as described above. The cells were transfected using the Fugene reagent, with 1.5 µg of pmCMV-G1 test plasmid, 0.7 µg of phCMV-MUP reference plasmid, and 24 µg of S or AS oligonucleotide.

Clonogenic and G418 survival assays

U2OS cells were seeded into 60 mm dishes (1 x 10⁵ cells per dish) in complete medium. After 48 h, cells were transfected as described above. Forty-eight hours after transfection, dishes were exposed to IR or UV-B, and G418 was added at 1 mg per ml in complete medium. G418-resistant cells were stained 10 days later with Coomassie Blue. To quantitate the outgrowth of drug-resistant cells, the Coomassie Blue-bound protein was solubilized at 37°C with 0.1 M NaOH, and the soluble material was analyzed by absorbance spectroscopy at a wavelength of 590 nm. For AT4BI cell survival assays, cells were transfected with pcDNA3.1, pcDNA3.1-FLAG-ATM, or HA-ATX. After 48 h, the transfected cells were exposed to the indicated doses of IR, and G418 was added at 8 hours post-irradiation. Drug-resistant colonies were stained with Coomassie Blue after 10 days in culture, and the samples were analyzed with Image Pro Plus software to quantitate cell density. For clonogenic assays where oligonucleotides were used, the cells were plated and transfected with S or AS oligonucleotides as described

above. Forty-eight hours after transfection, cells were exposed to IR or UV. Twenty-four hours after exposure to damaging agents, cells were replated at 1000 cells per 60 mm dish and colonies allowed to form for 10 days. Dishes were stained with Coomassie Blue, and the number of colonies (minimum size, 50 cells per colony) was counted by visual examination.

Example 6

Role of ATX in p53 activation

A major mediator of stress-induced signaling in mammalian cells is the tumor suppressor protein, p53 (Ko and Prives, Genes and Development 10:1054-1072, (1996); Ryan et al., Curr. Opin. Cell Biol. 13:332-337 (2001)). ATX phosphorylates p53 on Ser-15 (Figure 1C), a site implicated in the regulation of p53 stability and transcriptional activity (Dumaz and Meek, Curr. Opin. Cell Biol. 13:225-231 (1999); Zhang and Xiong, Science 292:1910-1915 (2001)). Therefore, the possibility that these two proteins are functionally linked during cellular stress responses was investigated. U2OS cells were transiently transfected with a HA-ATXWT or HA-ATXKI expression plasmid, together with a GFP-encoding plasmid to allow for FACS-based enrichment of the transfected cells. The GFP+ cells were then examined for IR-induced stabilization of p53, as well as for specific phosphorylation of this protein on Ser-15. Expression of ATXKI strongly suppressed both the phosphorylation of Ser-15 and the overall accumulation of p53 in IR-treated cells (Figure 3A). In contrast, overexpression of ATXWT enhanced both of these responses in cells exposed to IR. Consistent with findings presented above, treatment of U2OS cells with the AS oligonucleotide led to a decrease in endogenous ATX expression, and concomitantly reduced

both the phosphorylation and stabilization of p53 induced by IR exposure (Figure 3B). These results indicated that ATX exhibits functional overlap with ATM during IR-induced p53 activation.

5

Recent findings point toward ATM as a critical upstream regulator of the activity of the checkpoint kinase, hChk2, in IR-damaged cells (Ahn et al., Cancer Res. 60:5934-5936 (2000); Melchionna et al., Nat. Cell Biol. 2:762-765 (2000)). To determine whether ATX was also involved in hChk2 activation, the effect of AS oligonucleotide treatment on the IR-dependent phosphorylation of hChk2 was examined. In contrast to the p53 results, the AS-treated cells retained the ability to phosphorylate hChk2 in response to IR-induced stress (Figure 3B). These results indicate that, while ATM and ATX serve as positive regulators of p53 function, ATX plays no identifiable role as an upstream activator of a distinct ATM target protein, the hChk2 kinase. Moreover, the differential effects of AS treatment on p53 expression versus hChk2 activation argue against the possibility that AS exposure leads to nonspecific inhibition of checkpoint signaling responses to IR-induced DNA damage.

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Additional studies with AS oligonucleotide-treated cells demonstrated that, in contrast to ATM (Canman et al., Science 281, 1677-1679. 1998; Siliciano et al., Genes Dev 11, 3471-3481 (1997)), ATX plays a role in the phosphorylation and stabilization of p53 in cells exposed to UV light (Figure 3C). As observed with IR as the stress-inducing agent, a reduction in ATX protein expression severely impaired both Ser-15 phosphorylation and p53 protein accumulation in UV-damaged cells. The recognition of UV light-induced

30
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DNA damage occurs primarily during S phase, when pyrimidine dimers and other bulky lesions interfere with replication fork progression (Friedberg, DNA Repair and Mutagenesis (Washington, D.C., ASM Press) (1995); Lindahl and Wood, Cell 103:1121-1131 (1999)).

In order to further define the potential linkage between DNA replicational stress and ATX, the response of AS-treated cells to 5-fluorouracil (5-FU), an S-phase specific cytotoxic agent was examined (Danenberg et al., Seminars in Oncology 26:621-631 (1999); Grem, Investigational New Drugs 18:299-313 (2000)). Previous findings indicated that the cytotoxic effects of 5-FU are strongly p53-dependent (Bunz et al., J. Clin. Invest. 104:263-269 (1999)). Treatment of U2OS cells with 5-FU increased p53 expression to levels similar to those observed in UV-irradiated cells (Figure 3C). However, the accumulation of p53 induced by 5-FU exposure was not accompanied by an increase in Ser-15 phosphorylation. These findings indicate that the mechanism of p53 stabilization triggered by 5-FU does not involve upstream protein kinases that modify the Ser-15 site. Consistent with this conclusion, the level of p53 induction by 5-FU in AS-treated cells was identical to that observed in their S-treated counterparts. These results indicate that the inhibitory effect of the AS treatment on p53 activation is selective for those forms of stress that induce the phosphorylation of p53 at Ser-15.

Changes in phosphorylation at Ser-15 are typically accompanied by alterations in the expression of the p53 protein, which complicates the interpretation of results obtained by immunoblotting of whole cell extracts with phospho-Ser-15-specific antibodies. In order to confirm that reduced ATX expression interferes with

stress-induced Ser-15 phosphorylation, U2OS cells were transfected with either the S or AS oligonucleotide, and then were pretreated with the proteasome inhibitor, LLnV, to stabilize p53. In the presence of LLnV, the p53 level in each test population was relatively unaffected by UV exposure (data not shown). However, the ratio of phospho-Ser-15 to total p53 protein was increased by UV irradiation of both the mock-transfected and S oligonucleotide-treated cells. Although AS treatment partially interfered with the accumulation of p53 under these conditions, the reduction in ATX expression effectively blocked the stoichiometric increase in Ser-15 phosphorylation triggered by UV-induced stress.

Example 7

Role of ATX in IR-induced cell cycle arrest

Since p53 plays a central role in activation of the G1 checkpoint, and influences S, G2, and M checkpoints as well (Giaccia and Kastan, Genes & Development 12:2973-2983 (1998); Ko and Prives, *supra*, 1996), a functional deficiency of ATX might alter the cell-cycle arrest responses to IR and other genotoxic agents. To test this possibility, U2OS cells were pre-treated with S or AS oligonucleotides, exposed to IR, and cell-cycle distributions at 24 h post-irradiation were determined. In the absence of IR, AS treatment led to a reduction in the percentage of G1 phase cells, and a concomitant accumulation of G2/M phase cells, when compared to their S oligonucleotide-treated counterparts (Figure 3D). The AS-treated cells also contained an increased subpopulation with <2N DNA content, which is indicative of apoptotic cells. After IR exposure, cells treated with the S oligonucleotide accumulated in both G1 and G2/M phases and were cleared out of S phase, a

profile typical of p53-positive cells that retain G1 checkpoint function. In contrast, the AS-treated cells arrested primarily in G2/M phase after IR exposure. The cell-cycle distribution of the AS-treated cells was
5 reminiscent of that observed in cells that have lost p53-dependent checkpoint function (North and Hainaut, Pathol. Biol. 48:255-270 (2000); Waldman et al., Cancer Res. 55:5187-5190 (1995)). Immunoblot analyses of the same cell populations confirmed that AS exposure led to a
10 profound reduction in ATX protein levels in U2OS cells. In contrast, AS exposure caused no significant change in the expression levels of two control proteins, ATM and PLC- γ 1.

15 The cell-cycle distribution results described in Figure 3D demonstrated that ATX-deficient cells accumulate with 4N DNA content under both basal culture conditions and after IR-induced stress. This arrest state could reflect the activation of either a G2 or a
20 mitotic checkpoint (or both checkpoints). To distinguish between these possibilities, the effects of caffeine, a known inhibitor of the G2 checkpoint (Powell et al., Cancer Res. 55:1643-1648 (1995); Russell et al., Cancer Res. 55:1639-1642 (1995); Yao et al., Nat. Med.
25 2:1140-1143 (1996)), on the cell cycle distribution of the AS-treated cells were examined. The G2 checkpoint inhibitor was added to the culture medium at 8 h prior to harvest for determination of cell-cycle distributions (Figure 3E, *left panel*), and immunoblotting for ATX
30 expression (*right panel*). Caffeine completely reversed the accumulation of G2/M phase cells induced by AS treatment, indicating that ATX deficiency triggered the activation of a caffeine-sensitive G2 checkpoint. The immunoblotting results confirmed that AS-treated cells
35 displayed a marked, specific reduction in ATX protein

expression. In addition, treatment of the AS cells with caffeine also resulted in an increase in the percentage of hypodiploid cells, which indicates that an intact G2 checkpoint partially protects the ATX-deficient cells from apoptotic death, for example, by preventing a catastrophic entry into M phase.

Example 8

ATX overexpression complements IR sensitivity in ATM-deficient cells

Based on the finding that ATM and ATX display overlapping functions as activators of p53, it was investigated whether ATX overexpression can complement the phenotypic defects found in cells from A-T patients. One characteristic defect of cells from A-T patients is reduced clonogenic survival in culture, even in the absence of DNA dsb-inducing agents (Rotman and Shiloh, Oncogene 18:6135-6144 (1998)). As shown in Figure 4 A, transient transfection of ATM-null AT4BI cells with an ATM expression plasmid increased the outgrowth of G418-resistant colonies by approximately 2-fold, relative to cells transfected with empty vector. The clonogenic defect of AT4BI cells was partially rescued (approximately 1.5-fold increase in colony survival) by transient expression of ATX. Thus, ATX overexpression partially complements the intrinsic clonogenic survival defect of ATM-null cells. Furthermore, low-dose (1 Gy) IR treatment sharply reduced the clonogenic survival of mock-transfected AT4BI cells, and this radiosensitive phenotype was rescued to equivalent degrees by transfection of the cells with ATM or ATX (Figure 4B). Thus, overexpression of ATX complements, at least in part, the stress response defects observed in cells from A-T patients.

Example 9**Roles of ATX and ATM in hUpf1 phosphorylation and NMD**

The Upf1 helicase undergoes serum-inducible phosphorylation in intact cells, as demonstrated by two-dimensional (2-D) gel electrophoresis (Pal et al., *supra*, 2001). Based on the evidence disclosed herein that ATX is a UV-responsive kinase, the possibility that UV light exposure triggers the phosphorylation of hUpf1 in ATXWT-transfected U2OS cells was investigated. Serum stimulation or UV treatment induced virtually identical shifts in the 2-D electrophoretic mobility of hUpf1, which indicates that these agents provoke the phosphorylation of this protein at similar sites (data not shown). In contrast, expression of the catalytically-inactive ATXKI protein blocked the appearance of the most highly shifted form of hUpf1, and caused the accumulation of a broad band with intermediate electrophoretic mobility. The latter hUpf1 species can be less phosphorylated forms of the protein. Thus, overexpression of ATXKI interferes with both the serum- and UV-induced phosphorylation of hUpf1; however, these results also indicate that the hUpf1 is targeted by at least one additional protein kinase in these cells.

Based on the functional overlap between ATM and ATX during stress-induced p53 activation, it was possible that these PIKKs might also share the ability to regulate the RNA surveillance pathway leading to NMD. To focus our studies of hUpf1 phosphorylation on the Ser-Gln-rich region, a mammalian expression vector encoding GAL4 fused to the carboxyl terminus (amino acids 1019-1118) of hUpf1 (GAL4-hUpf11019-1118) was generated. Expression of GAL4-hUpf11019-1118 in U2OS cells generates a major immunoreactive band that migrates with a molecular mass

of ~35 kDa in serum-starved cells. Stimulation of the transfected cells with 10% fetal bovine serum or UV light leads to the increased expression of forms of GAL4-hUpf11019-1118 that display reduced electrophoretic mobility (Figure 5A, *left panel*). In this experiment, cells were harvested at 6 h after serum or UV exposure; however, the GAL4-hUpf11019-1118 mobility shifts could be detected as early as 2 h after cellular stimulation with either agent. The appearance of these shifted GAL4-hUpf11019-1118 bands is due to phosphorylation, as treatment of the cell extracts with λ phosphatase collapses the complex pattern of α -Gal4-reactive species into the major ~35 kDa band, which represents non-phosphorylated GAL4-hUpf11019-1118 (Figure 5A, *right panel*). Moreover, the observed GAL4-hUpf11019-1118 mobility shifts were due to phosphorylation of the hUpf1 fragment, as the electrophoretic mobility GAL4 alone was not altered by cellular exposure to serum or UV (Figure 5A, *lower panel*). In the experiment shown in Figure 5A (*left panel*), selected samples were pretreated with 20 μ M wortmannin in order to inhibit endogenous ATX and ATM kinase activities (Sarkaria et al., *supra*, 1998)). In the wortmannin-treated cells, the FBS- or UV-induced generation of the most slowly migrating form of GAL4-hUpf11019-1118 (indicated with an arrow) was preferentially inhibited. This drug effect was accompanied by an increase in the abundance of the less shifted bands, which can represent less phosphorylated forms of GAL4-hUpf11019-1118. These results indicate that, although a wortmannin-sensitive protein kinase(s) contributes to the inducible phosphorylation of the GAL4-hUpf11019-1118 reporter protein, the hUpf1 carboxyl-terminal region is also targeted for modification by at least one additional, wortmannin-resistant protein kinase.

To further examine the contributions of ATM and ATX to the phosphorylation of GAL4-hUpf11019-1118, U2OS cells were cotransfected with wild-type (WT) or kinase-inactive (KI) versions of HA-ATM or HA-ATX.

5 Expression of either HA-ATMKI or HA-ATXKI strongly suppressed the phosphorylation of GAL4-hUpf11019-1118 in cells treated with UV light (Figure 5B) or serum (data not shown). Expression of the catalytically active HA-ATMWT or HA-ATXWT proteins enhanced the

10 phosphorylation of GAL4-hUpf11019-1118 in both unstimulated and stimulated cells. The latter results add further support to the notion that ATX and ATM are capable of phosphorylating hUpf1 carboxyl-terminal region in intact cells. In these experiments, the HA-tagged ATM

15 and ATX proteins were overexpressed by approximately 2- and 1.5-fold, respectively, when compared to their endogenous counterparts (data not shown).

In addition, the effects of HA-ATXKI and

20 HA-ATMKI overexpression on NMD were comparatively examined using an established assay (Sun et al., Proc. Natl. Acad. Sci. USA 95:10009-1998). U2OS cells were transfected with a plasmid encoding either the normal human β -globin gene (Norm) or a mutated β -globin gene

25 bearing a premature termination codon (Ter), together with a reference plasmid encoding the mouse urinary protein (MUP). Where indicated, the cells were co-transfected with empty vector, or expression vectors encoding wild-type or kinase-inactive versions of ATM

30 (HA-ATMWT, HA-ATMKI) or ATX (HA-ATXWT, HA-ATXKI) (Figure 6A). Expression of the kinase-inactive HA-ATMKI or HA-ATXKI proteins abrogated NMD of the Ter-containing β -globin mRNA. Furthermore, treatment of the cells with the AS oligonucleotide to reduce endogenous ATX

35 expression confirmed that ATX expression is required for

maximal NMD activity under these assay conditions (Figure 6B). Collectively, these results indicate that ATM and ATX function as shared components of the pathways leading to both NMD and p53 activation during UV- and IR-induced stress.

Methods:

Construction of GST and GAL4-hUpf1 fusion proteins

The hUpf11019-1118-BamHI fragment was generated by PCR amplification of full-length hUpf1 using the following primers: 5'-AGGAGGGGATCCGGACGCCAGAAGAACCGCTTTGGG-3', 5'-AGGAGGGGATCCATACTGGGACAGCCCCGTCAC-3'. This fragment was subcloned into the BamHI site of pGEX-2T and pCMX-GAL4(N) to generate the GSThUpf11019-1118 and GAL4-hUpf11019-1118 fusion proteins, respectively.

GAL4-hUpf1 mobility shift assays

U2OS cells were plated in 60 mm dishes (4 x 10⁵ cells per dish), and then transfected with 0.5 µg pCMX-GAL4 or pCMX-GAL4-hUpf11019-1118, together with 4.5 µg pcDNA3.1-HA-ATXWT, HA-ATXKI, HA-ATMWT, or HA-ATMKI plasmid DNAs. The HA-ATMKI protein contains an Asp-2870>Ala mutation that inactivates the kinase domain. Twenty hours after transfection, serum was removed from the medium, and the cells were cultured for an additional 24 h. The cells were then treated with 10% fetal bovine serum or 100 J/m² UV-B. Where indicated, the serum-starved cells were pretreated for 30 min with 20 µM wortmannin prior to treatment with serum or UV. Cells were harvested in lysis buffer containing 25 mM Hepes, pH 7.4, 300 mM NaCl, 1.5 mM MgCl₂, 1 mM EGTA, 1% Triton X-100, 20 mM β-glycerophosphate, 20 nM microcystin, 0.1 mM sodium orthovanadate, 1 mM DTT, plus protease inhibitors. For phosphatase treatment, 600 U λ phosphatase was added to cellular extracts (New England

Biolabs). Cell extracts were resolved on by SDS-PAGE, and were immunoblotted with α -GAL4 antibody.

RNA isolation and assays of NMD

5 Total or nuclear RNA was isolated using Trizol (Invitrogen) or the NE-PER kit (Pierce), respectively. The extent of NMD was determined by using RT-PCR to quantitate the levels of Globin and MUP mRNA as described previously (Ishigaki et al., Cell 83: 1-4 (2001)), except
10 that 21 cycles of PCR were used when analyzing the effects of ATX-specific S and AS oligonucleotides.

Example 10

Decreased Expression of ATX Results in Spontaneously

Increased DNA Damage

U2OS osteosarcoma cells were treated with small-interfering (si) RNA directed against luciferase (control) or ATX. The siRNA consistently induces a >80%
20 decrease in the expression of ATX protein at day 3 post-transfection. The transfected cells were treated with 0, 3, or 10 Gy ionizing radiation (IR), and then lysed after either 1 hour or 18 hours. The cell extracts were separated by SDS-PAGE and immunoblotted with an
25 anti-phospho-Histone H2AX antibody. A significant increase in phospho-Histone H2AX immunoreactivity in 0 Gy IR-treated cells exposed to the ATX siRNA relative to the corresponding luciferase siRNA-transfected control cells was detected (see Figure 7). The level of a control
30 polypeptide, α -tubulin, was also determined to show equal loading of each lane.

The appearance of phospho-Histone H2AX marks DNA double-strand breaks or other forms of DNA damage, as
35 indicated by the strong induction of immunoreactivity in

IR-treated cells. These results indicate that
ATX-deficient cells can spontaneously develop DNA damage.
Furthermore, the compromised phosphorylation of Histone
H2AX observed in IR-treated, ATX-deficient cells
5 indicates that loss of ATX function can also compromise
DNA damage recognition and/or repair in mammalian cells.

Throughout this application various
publications have been referenced within parentheses.
10 The disclosures of these publications in their entireties
are hereby incorporated by reference in this application
in order to more fully describe the state of the art to
which this invention pertains.

15 Although the invention has been described with
reference to the disclosed embodiments, those skilled in
the art will readily appreciate that the specific
experiments detailed are only illustrative of the
invention. It should be understood that various
20 modifications can be made without departing from the
spirit of the invention.

What is claimed is:

1. An isolated nucleic acid molecule,
comprising substantially the same nucleotide sequence as
5 SEQ ID NO:1.
2. The isolated nucleic acid molecule of claim
1, wherein said nucleic acid molecule encodes an ATX
polypeptide comprising an amino acid sequence shown in
10 SEQ ID NO:2.
3. A vector, comprising the isolated nucleic
acid molecule of claim 1.
- 15 4. A host cell, comprising the vector of claim
3.
5. A method of producing an ATX polypeptide
comprising:
20
 - a) growing the host cell according to claim 4
under conditions appropriate for expression of the ATX
polypeptide, and
 - 25 b) isolating the ATX polypeptide from the host
cell or host cell growth medium.
6. An isolated oligonucleotide, comprising at
least 15 contiguous nucleotides of a nucleotide sequence
30 referenced as SEQ ID NO:11.
7. An isolated polypeptide, comprising
substantially the same amino acid sequence as SEQ ID
NO:2.
35

8. The polypeptide of claim 7, wherein said polypeptide comprises an amino acid sequence as referenced in SEQ ID NO:2.

5 9. An antibody, or antigen binding fragment thereof, which specifically binds to an ATX polypeptide comprising an amino acid sequence as referenced in SEQ ID NO:2.

10 10. A method for identifying a compound that specifically binds to an ATX polypeptide of claim 7, comprising:

15 a) contacting said ATX polypeptide with a compound, and

 b) determining specific binding of said compound to said ATX polypeptide.

20 11. The method of claim 10, wherein said compound is a polypeptide.

25 12. A method for identifying an ATX-modulatory compound, comprising measuring the level of an ATX polypeptide in the presence of a test compound, wherein a difference in the level of said ATX polypeptide in the presence of said test compound compared to in the absence of said test compound indicating that said test compound is an ATX-modulatory compound, and wherein said
30 ATX-modulatory compound is not caffeine or wortmannin.

 13. The method of claim 12, wherein said ATX-modulatory compound decreases the level of ATX polypeptide.

14. The method of claim 12, wherein said ATX-modulatory compound increases the level of ATX polypeptide.

5 15. The method of claim 12, wherein said level of ATX polypeptide is measured by determining the kinase activity of said ATX polypeptide.

10 16. The method of claim 12, wherein said level of ATX polypeptide is measured by determining the phosphorylation of a p53 polypeptide or fragment.

15 17. The method of claim 12, wherein said level of ATX polypeptide is measured by determining the level of p53 polypeptide accumulation.

20 18. The method of claim 12, wherein said level of ATX polypeptide is measured by determining the level of non-sense mediated messenger RNA (mRNA) decay (NMD).

 19. The method of claim 12, wherein said ATX-modulatory compound is an interfering RNA.

25 20. A method for modulating cell survival, comprising introducing a compound identified by the method of claim 12 into a cell in an amount effective to modulate survival of said cell.

30 21. The method of claim 20, wherein said compound decreases cell survival.

 22. The method of claim 20, wherein said compound increases cell survival.

23. The method of claim 20, wherein said cell is exposed to a stressor agent.

24. The method of claim 23, wherein said
5 stressor agent is selected from the group consisting of:
UV light, ionizing radiation, and a chemical agent.

25. A method for decreasing cell survival,
comprising introducing the antisense oligonucleotide
10 according to claim 6 into a cell in an amount effective
to decrease survival of said cell.

A

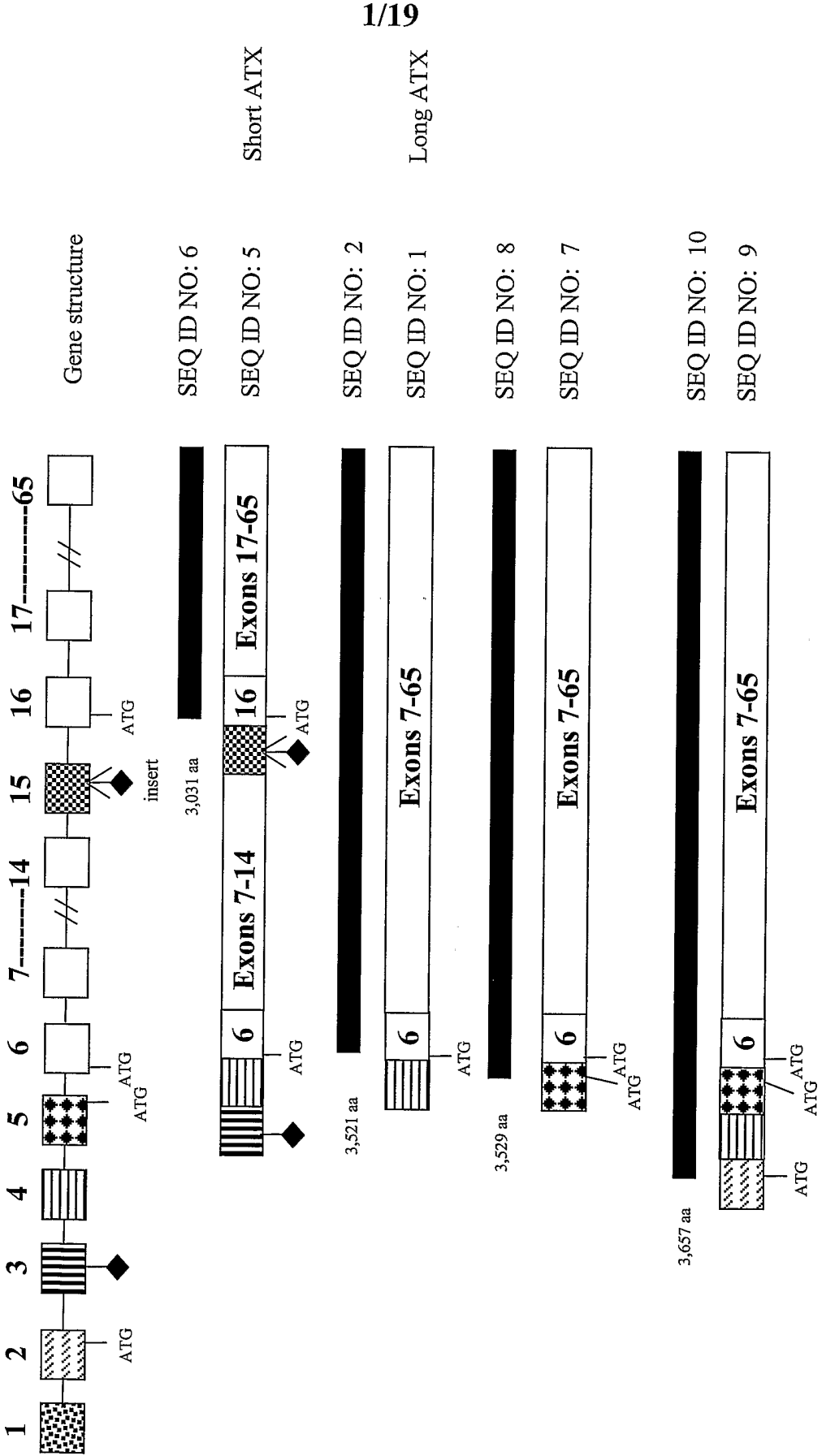
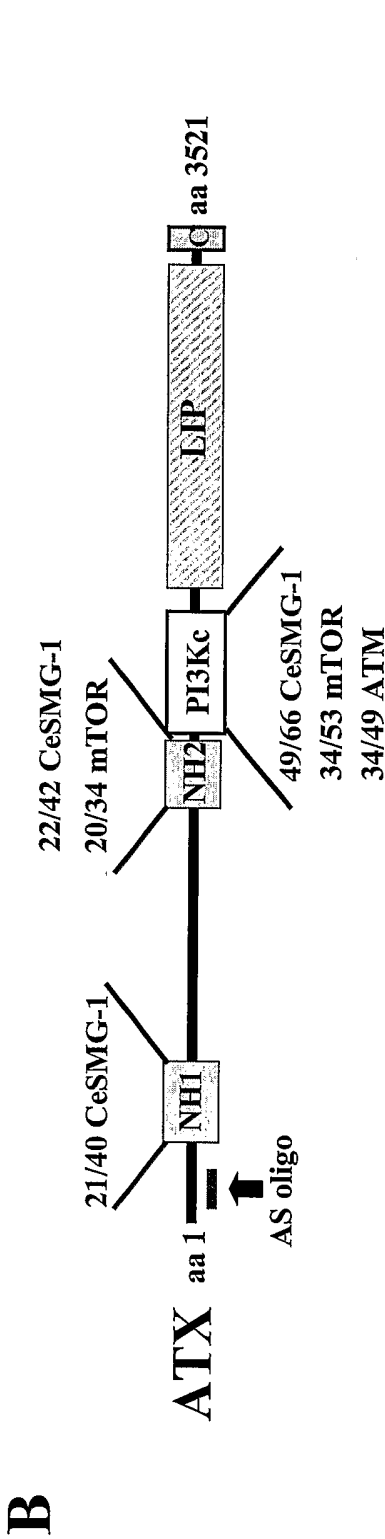


Figure 1



PI 3-K catalytic domain

ATX	2004	GSDGKSYPLPKGLEDLHDERIMQFLSTVNTMFAT---	INRQETPRFFARHYSVTPGLTSGSLIQWVDGATPLF-----	GLYKRWQORE-AALQAAQ
CeSMG-1	1774	GSDGKQVAFLFKGREDLHDERVMQFLRLCNVMLQPKGKHRSVAAVQAHHYAVIPGLGPRSGLIKWVEGATPMF-----	HIYRKKWQME-KALKQA	
mTOR	2176	GSNGHEFVFLKKGHEDLRQDERVMQLFGLVNTLLAN---	DPTSLRKNLSIQRYAVLPLSTNSGLIGWPHCDTLH-----	ALLRDYREKK-K-----
ATM	2706	GSDGKERQIVKGRDDLQDAVMQQVQMCNTLLQR---	NTETRKRKLITCTYKVVVPLSQSGVLEWCTGTVPITGEFLVNNEDGAHKRYRPNDFSAFQCC	
ATX		KAQDSYQTPQNPGLVPRPSELVYSKIGPALKT--	VGLSLDVSRDWDPLHVMKAVLEELMEATPPNLLAKELWSSCTTPDEWWRVTQSYARSTAVMSMVG	
CeSMG-1		TKKNGETVPE----	IERPSNMVYHNMIRLA FADHKIDSSITSDRSKWPAEILIEEVFESLTAKTPTDLISRELWMRANDATTWMSVTKRYSRSLAVMSMVG	
mTOR		-----	LLNIEHRIMLRMAPDXYDHLTLMQKVE-----	VFEHAVNNTAGDDLAKLLMLKSPSSEVWFDRRTNYTRSLAVMSMVG
ATM		KKMMEVQK-----	KSFEKYE-----	VFMDVCONFQVVF-RYFCMEKFID-----
ATX		YIIIGLGRHLDNVLIDMTTGEVVHIDYNVCFEKGKSLRVPEKPFPRMTQNIETALGVTVGEVFRLSCEQVLIHMRRGRETIITLLEAFVYDPLVDWT	2286	
CeSMG-1		SVLGLGRHLDNLLVDLKWGHVVHIDYNICFDKGNLRI PETVPPRLTRNMRRHALGPSEMYGTFRSCVHVLSLIRSGHQLTMLLIDAFVDFDPLVDWT	2057	
mTOR		YILLGLGRHP SNLMLDRLSGKILIHIDFGCFEVA MEKFKPELPRLTRMLITMA MEVTLGDGNYRIITCHTIVMEVLRHKDSVMAVTEAFVYDPLINWR	2429	
ATM		YILLGLGRHVQNILINEQSAELVHIDLGVAFEQGIKILPTPETVPPERLIPRDI VDGMGITGVEGFRRCCEKTMFVNRNSQETLITIVELLVDPLDFDWT	2961	

Figure 1

C

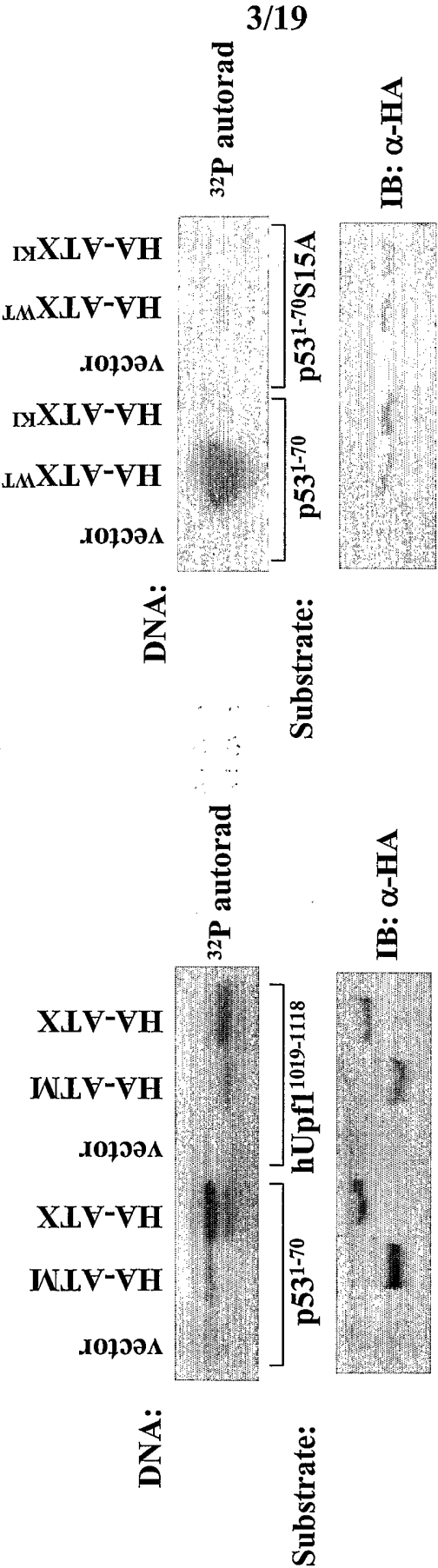


Figure 1

D

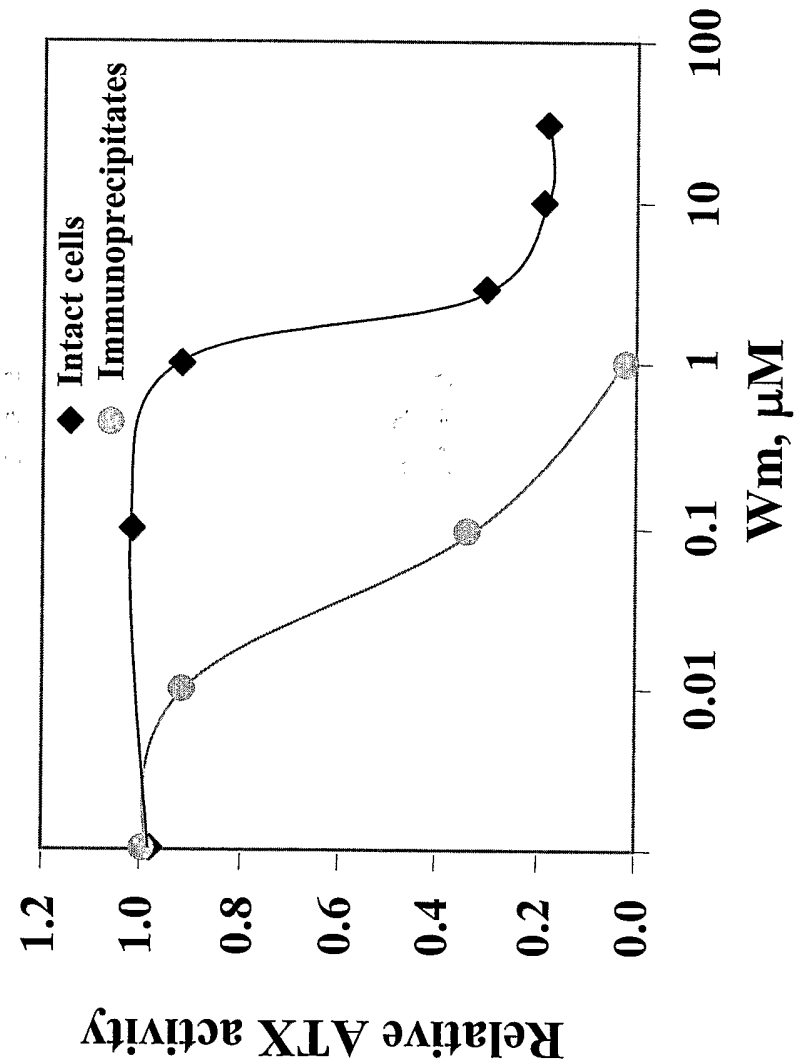


Figure 1

A

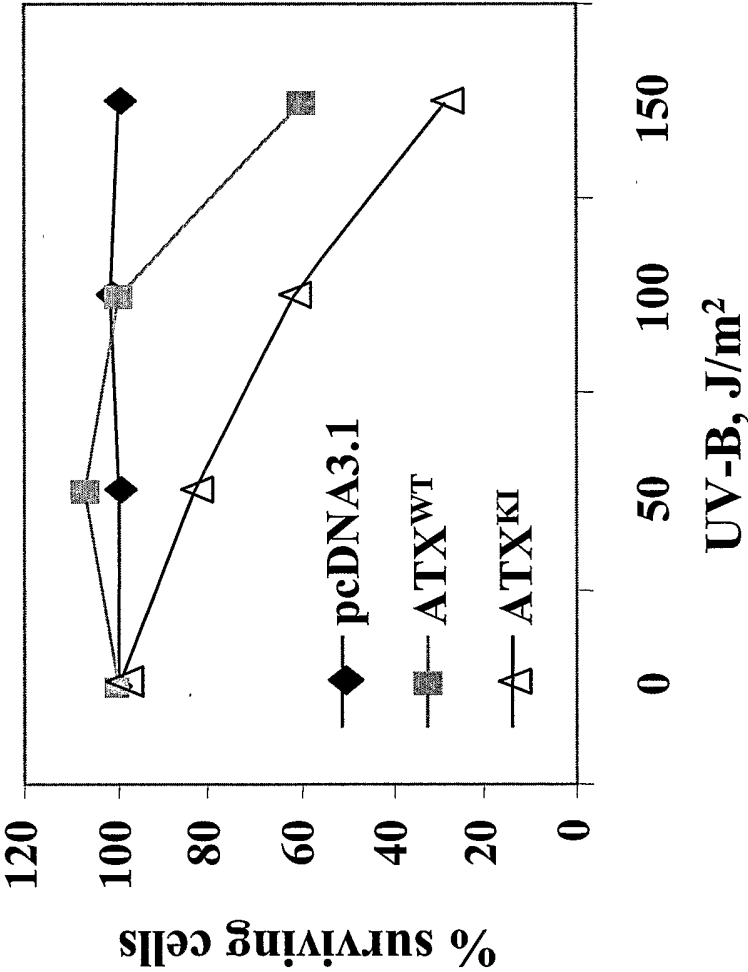


Figure 2

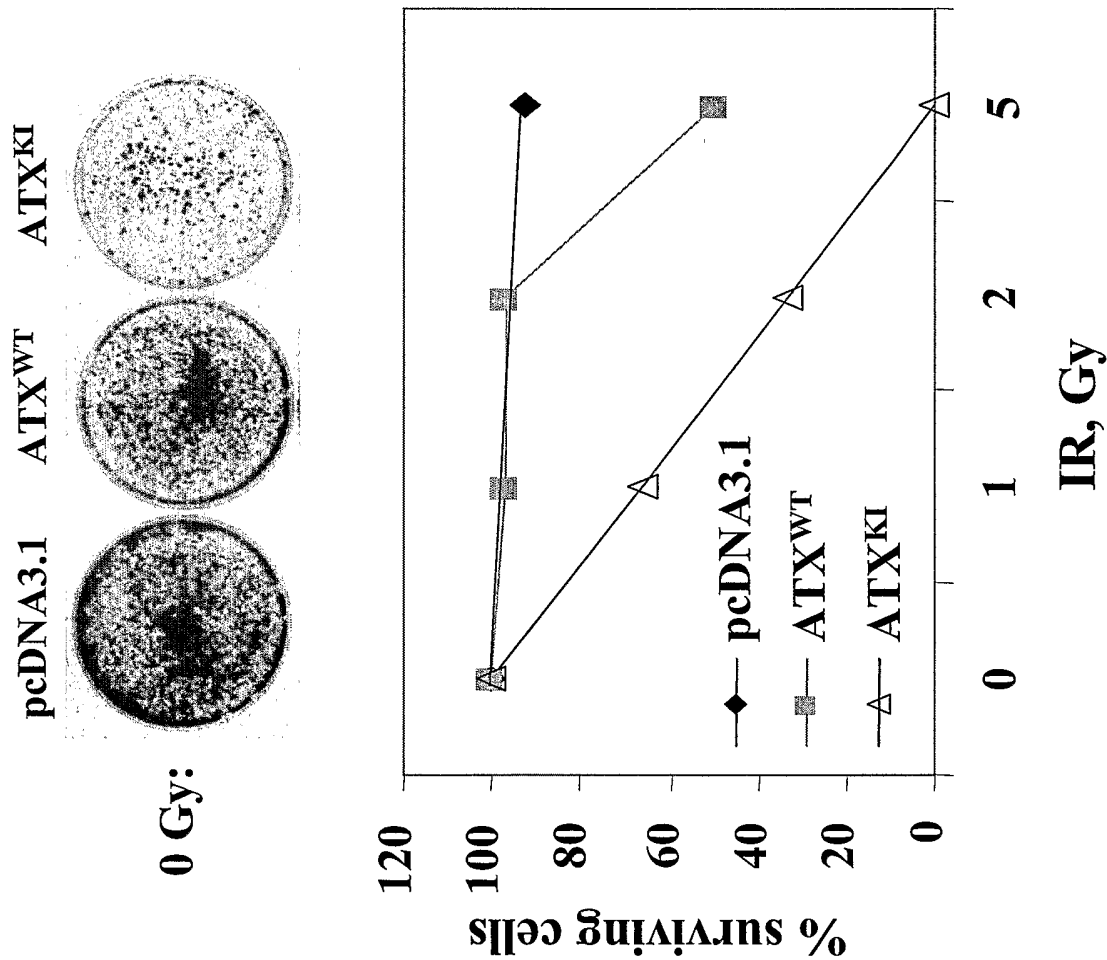


Figure 2

7/19

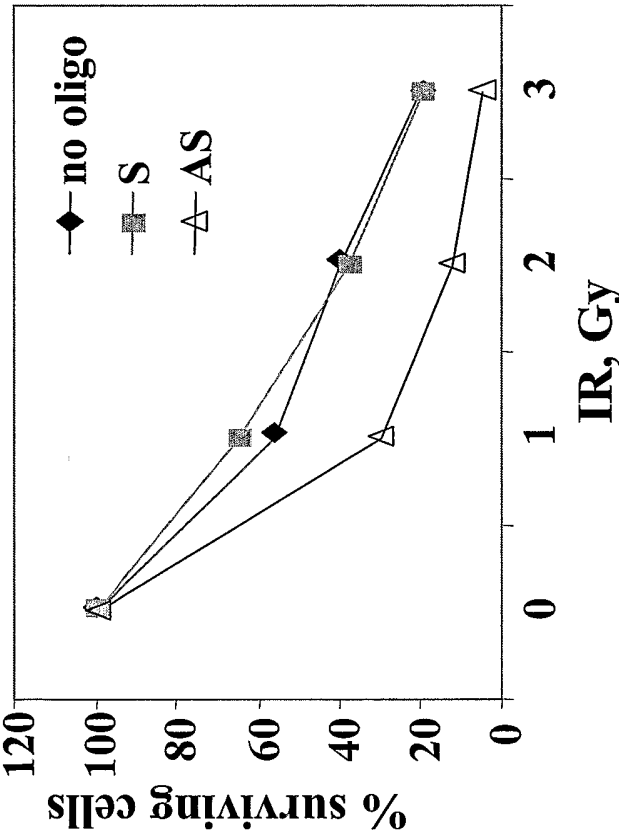
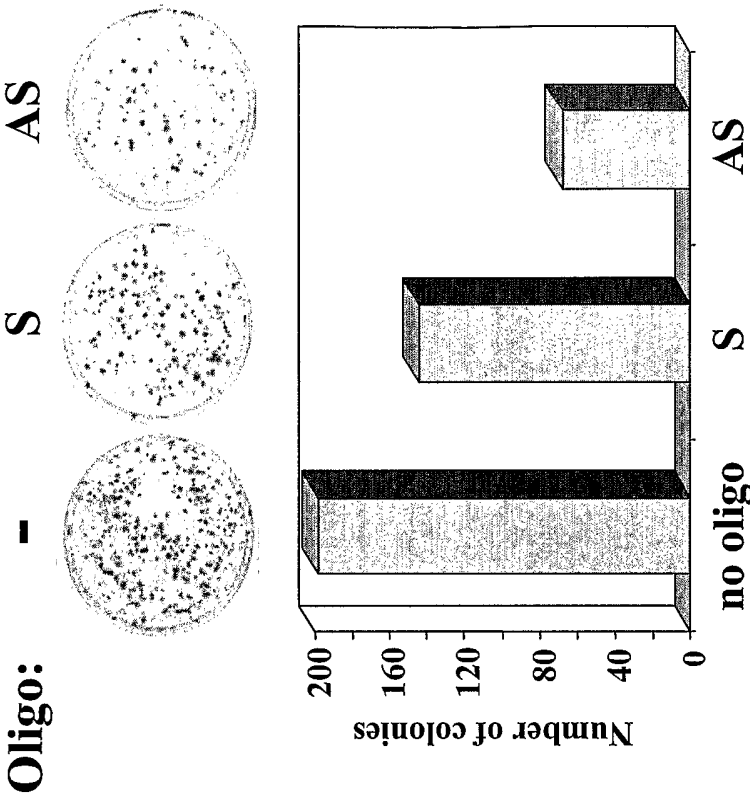


Figure 2

A

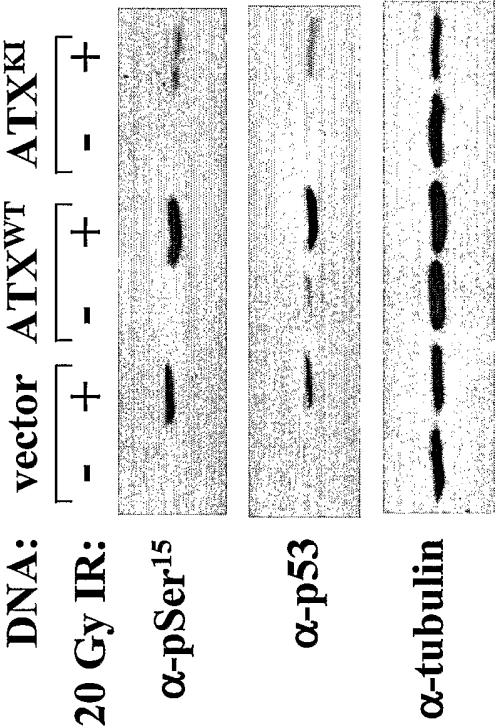


Figure 3

B

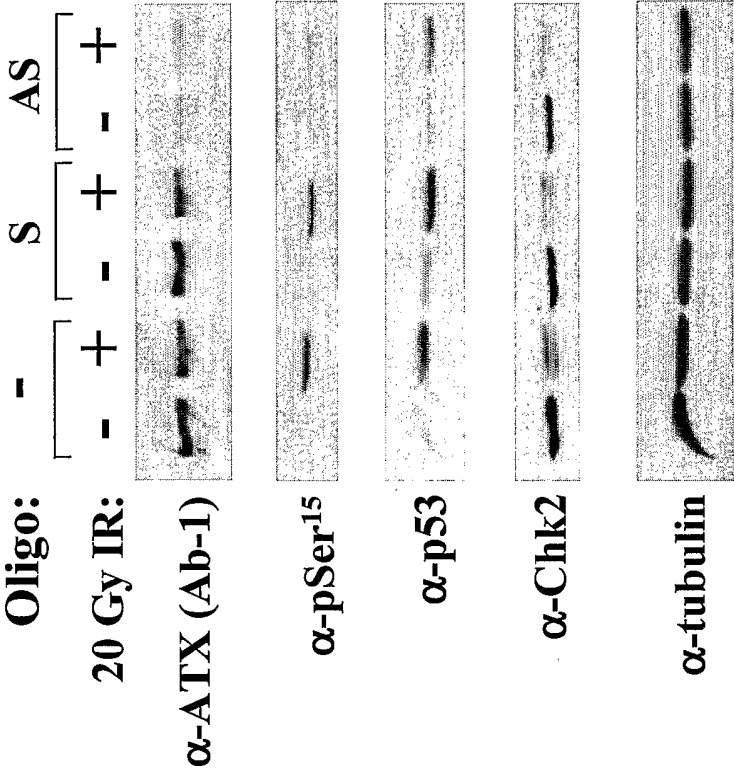


Figure 3

C

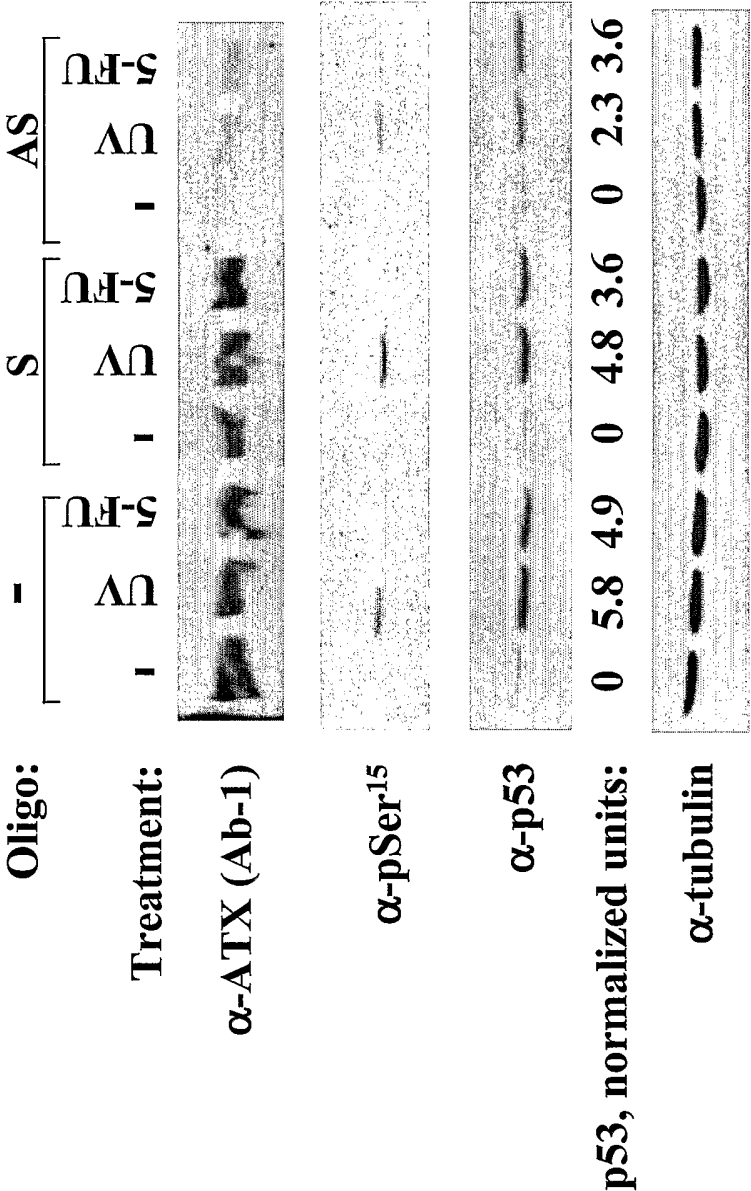
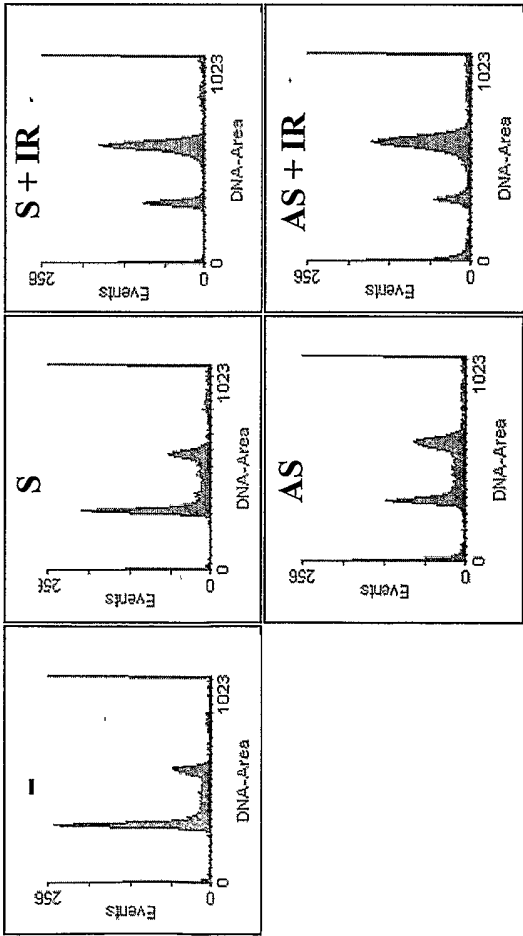
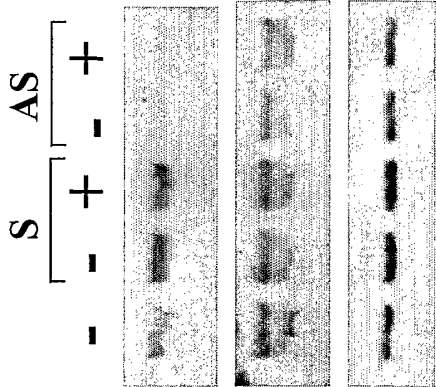


Figure 3

D



Oligo:
20 Gy IR:
 α -ATX (Ab-1)
 α -ATM
 α -PLC γ 1



	Sub-G ₁	G ₁	S	G ₂ /M
no oligo	12.5	51.5	14.6	21.3
S	6.7	48.1	16.2	29.0
S + IR	9.1	21.4	2.5	67.0
AS	25.7	25.3	14.3	34.7
AS + IR	29.4	10.7	3.9	56.0

Figure 3

E

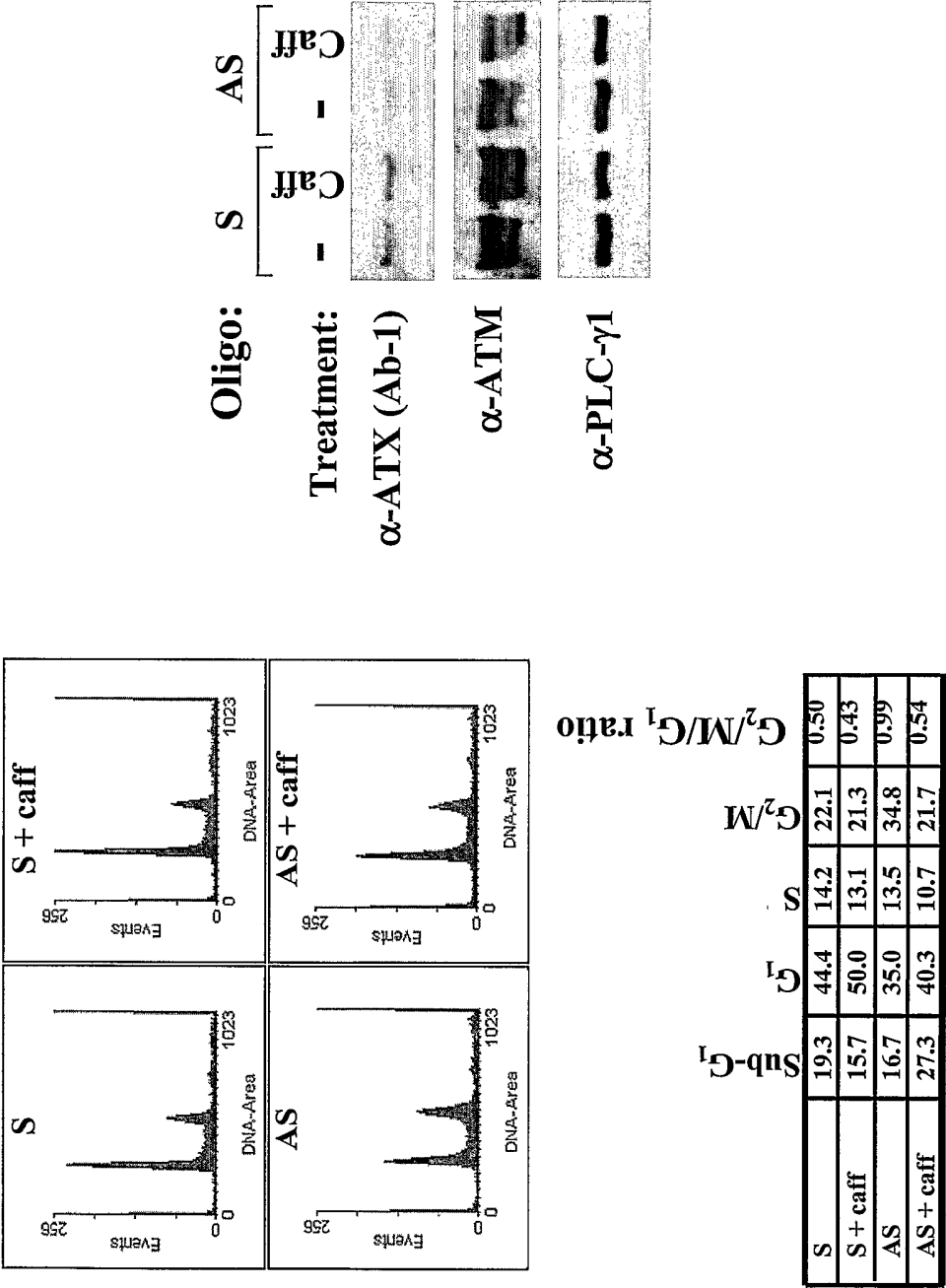


Figure 3

A

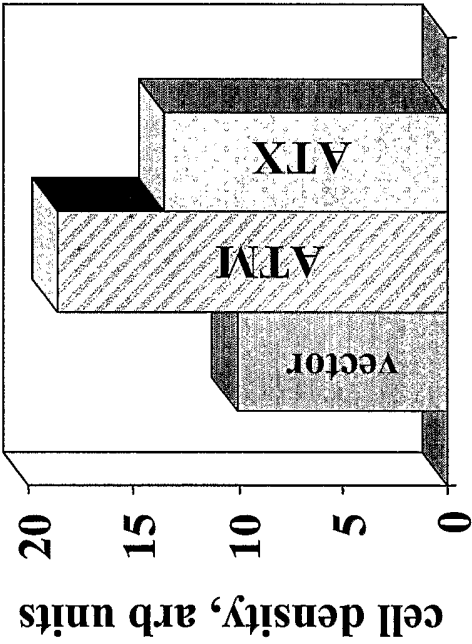
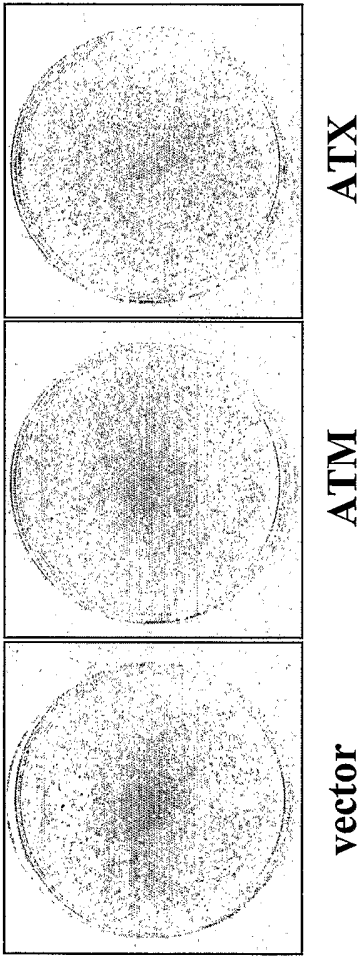


Figure 4

B

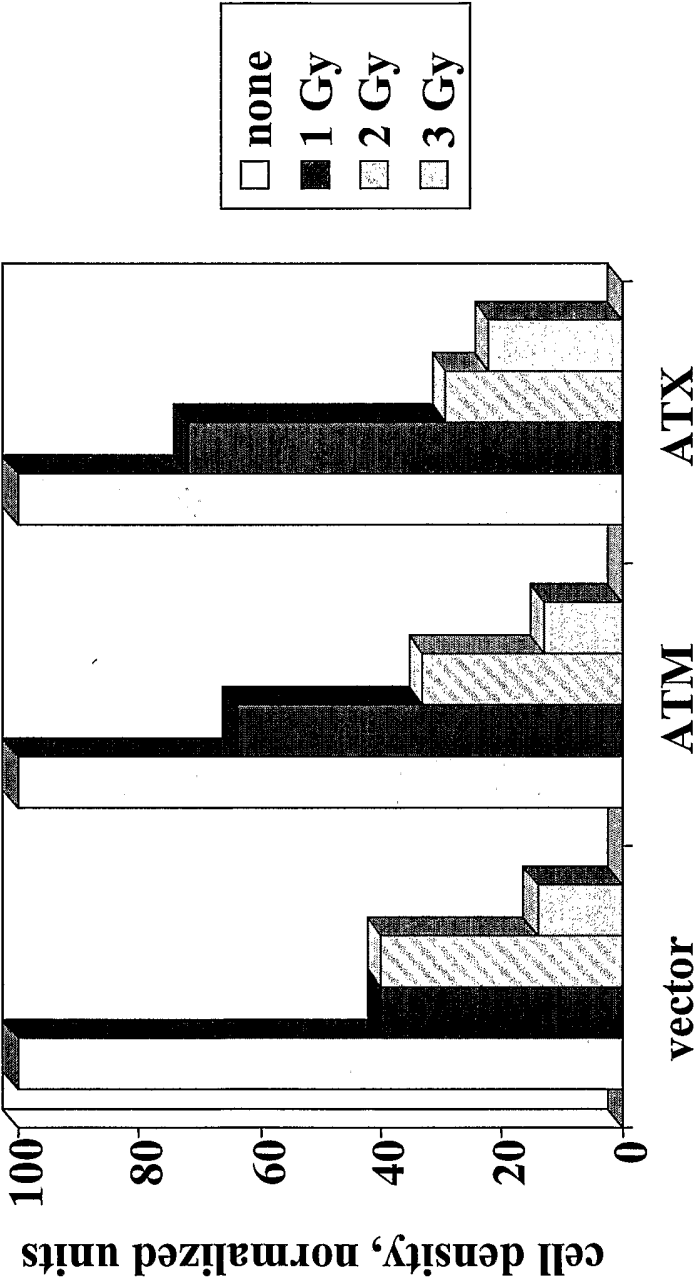


Figure 4

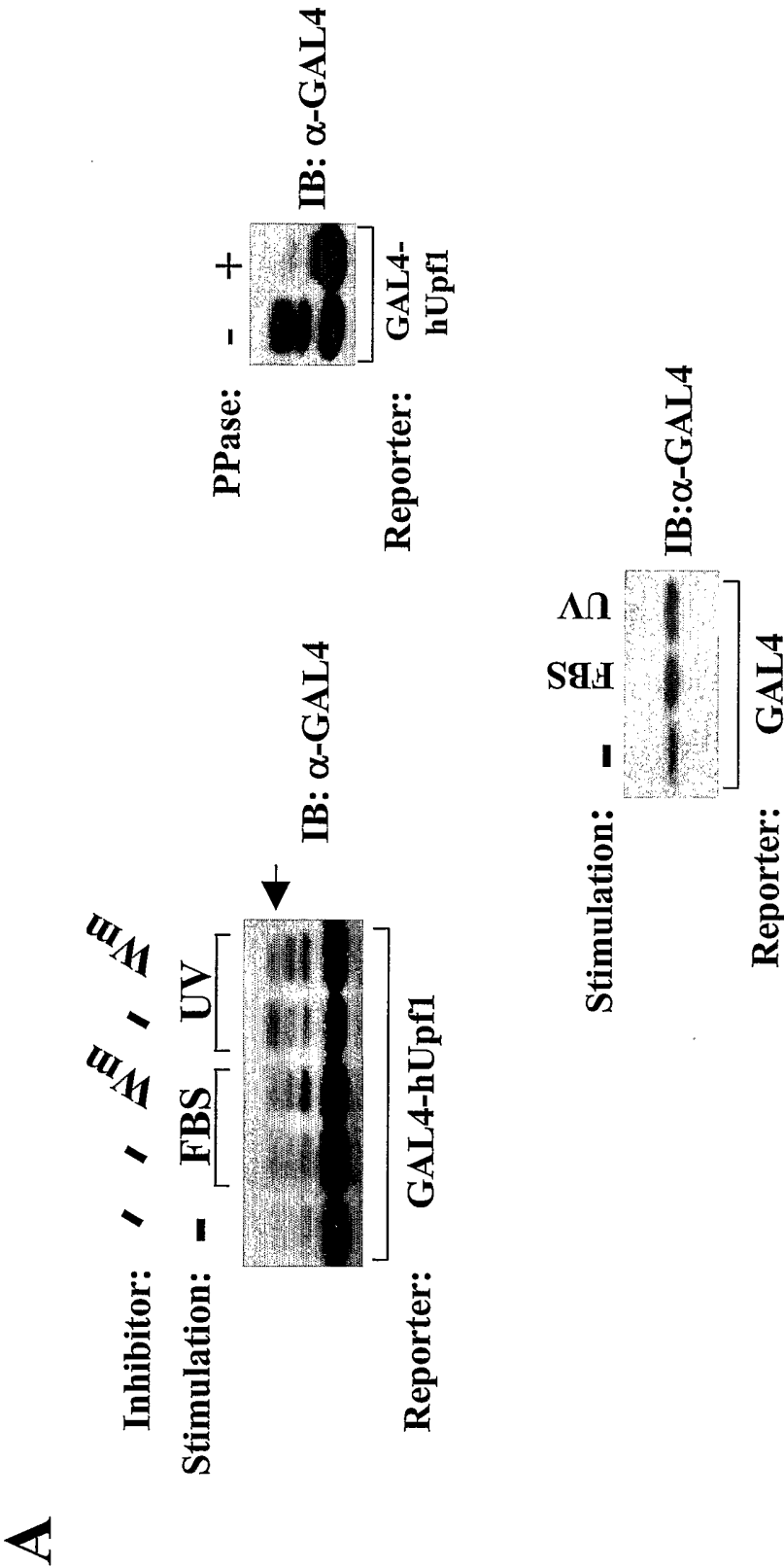


Figure 5

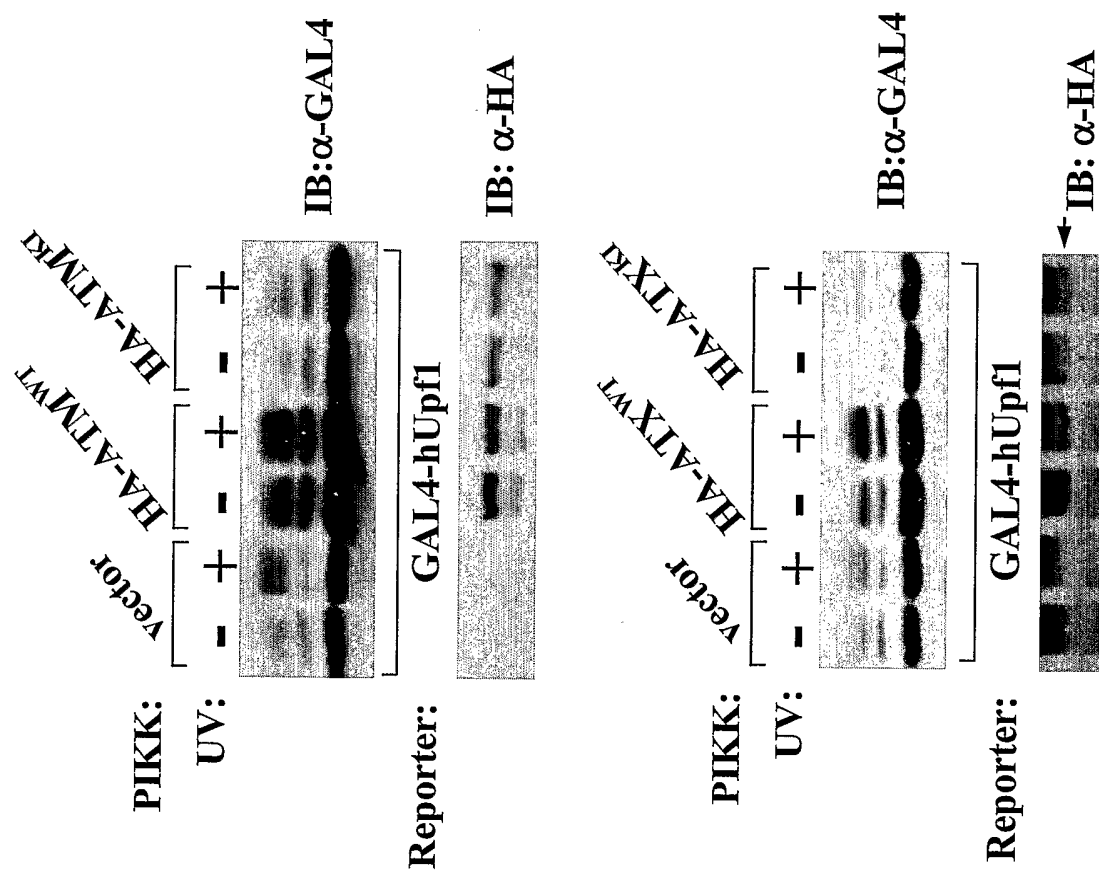
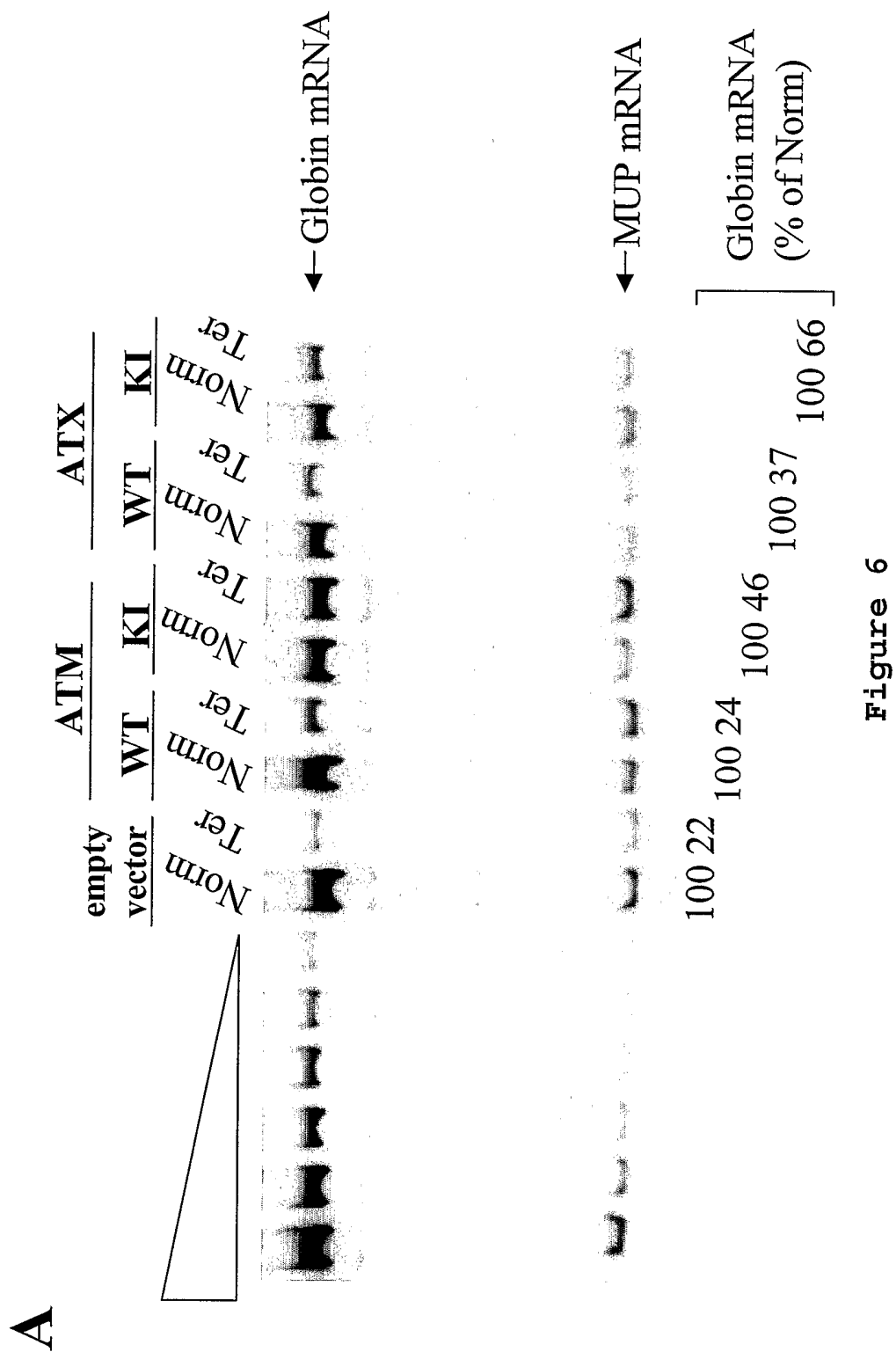


Figure 5



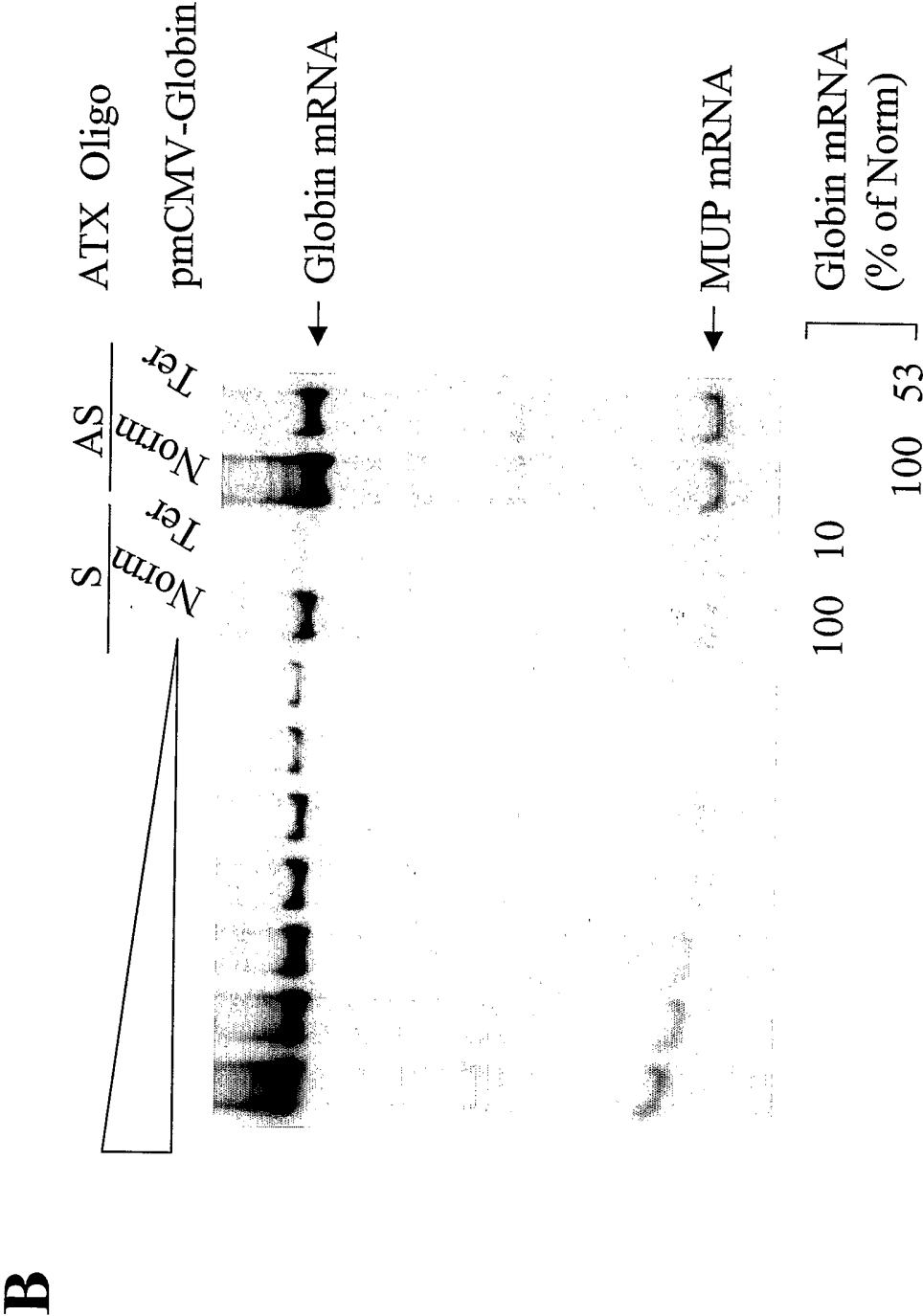


Figure 6

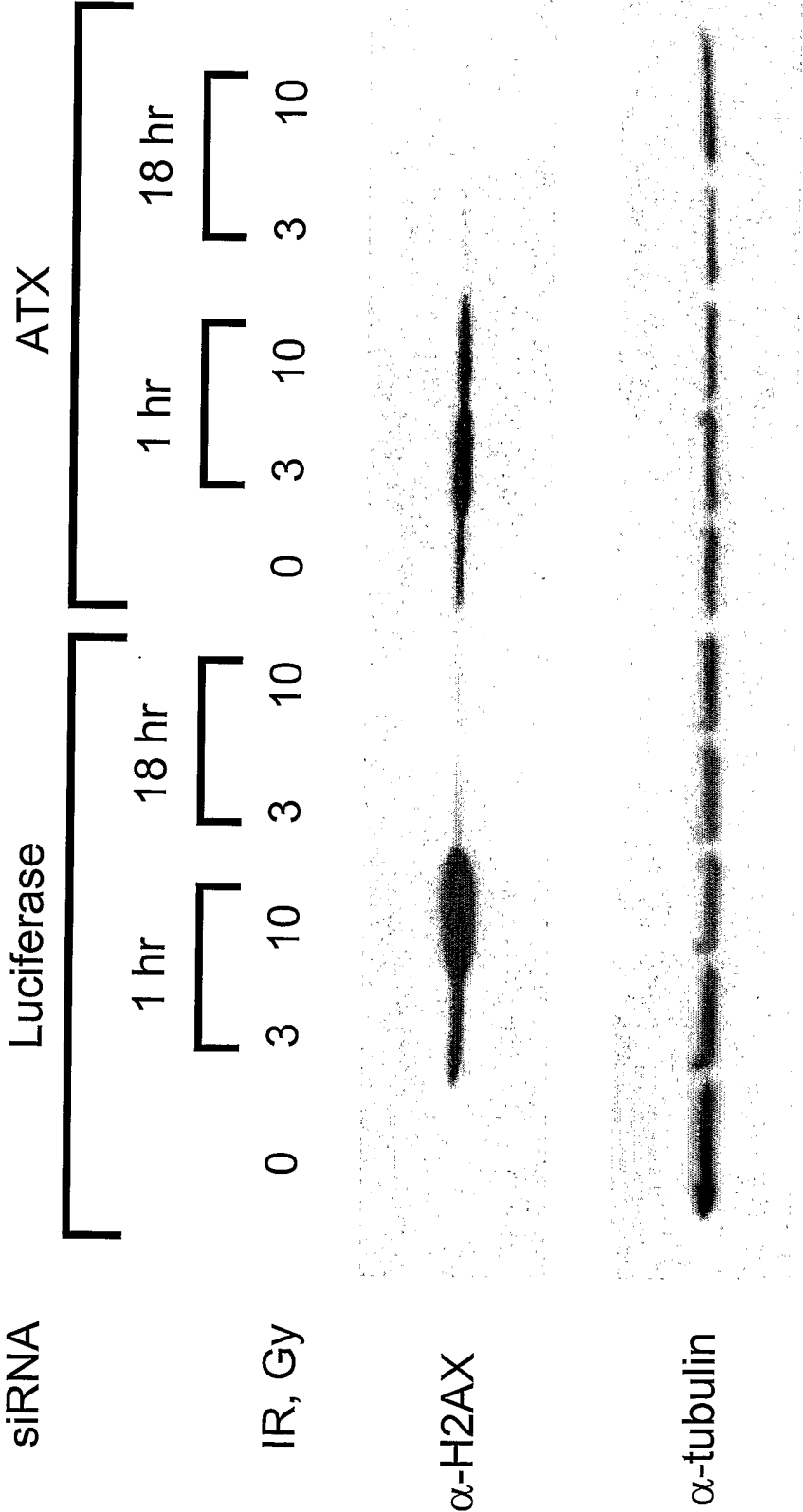


Figure 7

SEQUENCE LISTING

<110> The Burnham Institute
Duke University

<120> ATM Related Kinase ATX, Nucleic Acids
Encoding Same and Methods of Use

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<150> 10/165,216

<151> 2002-06-06

<160> 11

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 12464

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (91)...(10656)

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Met Ser Tyr Cys Asp Glu Ser Arg
1 5

ctg tcg aat ctt ctt cgg agg atc acc cgg gaa gac gac aga gac cga 162
Leu Ser Asn Leu Leu Arg Arg Ile Thr Arg Glu Asp Asp Arg Asp Arg
10 15 20

aga ttg gct act gta aag cag ttg aaa gaa ttt att cag caa cca gaa 210
Arg Leu Ala Thr Val Lys Gln Leu Lys Glu Phe Ile Gln Gln Pro Glu
25 30 35 40

aat aag ctg gta cta gtt aaa caa ttg gat aat atc ttg gct gct gta 258
Asn Lys Leu Val Leu Val Lys Gln Leu Asp Asn Ile Leu Ala Ala Val
45 50 55

cat gac gtg ctt aat gaa agt agc aaa ttg ctt cag gag ttg aga cag 306
His Asp Val Leu Asn Glu Ser Ser Lys Leu Leu Gln Glu Leu Arg Gln
60 65 70

gag gga gct tgc tgt ctt ggc ctt ctt tgt gct tct ctg agc tat gag 354
Glu Gly Ala Cys Cys Leu Gly Leu Leu Cys Ala Ser Leu Ser Tyr Glu
75 80 85

gct gag aag atc ttc aag tgg att ttt agc aaa ttt agc tca tct gca 402

Ala	Glu	Lys	Ile	Phe	Lys	Trp	Ile	Phe	Ser	Lys	Phe	Ser	Ser	Ser	Ala	
90						95					100					
aaa	gat	gaa	gtt	aaa	ctc	ctc	tac	tta	tgt	gcc	acc	tac	aaa	gca	cta	450
Lys	Asp	Glu	Val	Lys	Leu	Leu	Tyr	Leu	Cys	Ala	Thr	Tyr	Lys	Ala	Leu	
105					110					115					120	
gag	act	gta	gga	gaa	aag	aaa	gcc	ttt	tca	tct	gta	atg	cag	ctt	gta	498
Glu	Thr	Val	Gly	Glu	Lys	Lys	Ala	Phe	Ser	Ser	Val	Met	Gln	Leu	Val	
				125					130					135		
atg	acc	agc	ctg	cag	tct	att	ctt	gaa	aat	gtg	gat	aca	cca	gaa	ttg	546
Met	Thr	Ser	Leu	Gln	Ser	Ile	Leu	Glu	Asn	Val	Asp	Thr	Pro	Glu	Leu	
			140					145					150			
ctt	tgt	aaa	tgt	gtt	aag	tgc	att	ctt	ttg	gtg	gct	cga	tgt	tac	cct	594
Leu	Cys	Lys	Cys	Val	Lys	Cys	Ile	Leu	Leu	Val	Ala	Arg	Cys	Tyr	Pro	
		155					160					165				
cat	att	ttc	agc	act	aat	ttt	agg	gat	aca	gtt	gat	ata	tta	gtt	gga	642
His	Ile	Phe	Ser	Thr	Asn	Phe	Arg	Asp	Thr	Val	Asp	Ile	Leu	Val	Gly	
	170					175					180					
tgg	cat	ata	gat	cat	act	cag	aaa	cct	tcg	ctc	acg	cag	cag	gta	tct	690
Trp	His	Ile	Asp	His	Thr	Gln	Lys	Pro	Ser	Leu	Thr	Gln	Gln	Val	Ser	
185					190					195					200	
ggg	tgg	ttg	cag	agt	ttg	gag	cca	ttt	tgg	gta	gct	gat	ctt	gca	ttt	738
Gly	Trp	Leu	Gln	Ser	Leu	Glu	Pro	Phe	Trp	Val	Ala	Asp	Leu	Ala	Phe	
			205						210					215		
tct	act	act	ctt	ctt	ggc	cag	ttt	ctg	gaa	gac	atg	gaa	gca	tat	gct	786
Ser	Thr	Thr	Leu	Leu	Gly	Gln	Phe	Leu	Glu	Asp	Met	Glu	Ala	Tyr	Ala	
			220					225					230			
gag	gac	ctc	agc	cat	gtg	gcc	tct	ggg	gaa	tca	gtg	gat	gaa	gat	gtc	834
Glu	Asp	Leu	Ser	His	Val	Ala	Ser	Gly	Glu	Ser	Val	Asp	Glu	Asp	Val	
		235					240					245				
cct	cct	cca	tca	gtg	tca	tta	cca	aag	ctg	gct	gca	ctt	ctc	cgg	gta	882
Pro	Pro	Pro	Ser	Val	Ser	Leu	Pro	Lys	Leu	Ala	Ala	Leu	Leu	Arg	Val	
		250				255					260					
ttt	agt	act	gtg	gtg	agg	agc	att	ggg	gaa	cgc	ttc	agc	cca	att	cgg	930
Phe	Ser	Thr	Val	Val	Arg	Ser	Ile	Gly	Glu	Arg	Phe	Ser	Pro	Ile	Arg	
265					270					275					280	
ggc	cct	cca	att	act	gag	gca	tat	gta	aca	gat	gtt	ctg	tac	aga	gta	978
Gly	Pro	Pro	Ile	Thr	Glu	Ala	Tyr	Val	Thr	Asp	Val	Leu	Tyr	Arg	Val	
				285					290					295		
atg	aga	tgt	gtg	acg	gct	gca	aac	cag	gtg	ttt	ttt	tct	gag	gct	gtg	1026
Met	Arg	Cys	Val	Thr	Ala	Ala	Asn	Gln	Val	Phe	Phe	Ser	Glu	Ala	Val	
			300					305					310			

ttg aca gct gct aat gag tgt gtt ggt gtt ttg ctc ggc agc ttg gat	1074
Leu Thr Ala Ala Asn Glu Cys Val Gly Val Leu Leu Gly Ser Leu Asp	
315 320 325	
cct agc atg act ata cat tgt gac atg gtc att aca tat gga tta gac	1122
Pro Ser Met Thr Ile His Cys Asp Met Val Ile Thr Tyr Gly Leu Asp	
330 335 340	
caa ctg gag aat tgc cag act tgt ggt acc gat tat atc atc tca gtc	1170
Gln Leu Glu Asn Cys Gln Thr Cys Gly Thr Asp Tyr Ile Ile Ser Val	
345 350 355 360	
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Leu Asn Leu Leu Thr Leu Ile Val Glu Gln Ile Asn Thr Lys Leu Pro	
365 370 375	
tca tca ttt gta gaa aaa ctg ttt ata cca tca tct aaa cta cta ttc	1266
Ser Ser Phe Val Glu Lys Leu Phe Ile Pro Ser Ser Lys Leu Leu Phe	
380 385 390	
ttg cgt tat cat aaa gaa aaa gag gtt gtt gct gta gcc cat gct gtt	1314
Leu Arg Tyr His Lys Glu Lys Glu Val Val Ala Val Ala His Ala Val	
395 400 405	
tat caa gca gtg ctc agc ttg aag aat att cct gtt ttg gag act gcc	1362
Tyr Gln Ala Val Leu Ser Leu Lys Asn Ile Pro Val Leu Glu Thr Ala	
410 415 420	
tat aag tta ata ttg gga gaa atg act tgt gcc cta aac aac ctc cta	1410
Tyr Lys Leu Ile Leu Gly Glu Met Thr Cys Ala Leu Asn Asn Leu Leu	
425 430 435 440	
cac agt cta caa ctt cct gag gcc tgt tct gaa ata aaa cat gag gct	1458
His Ser Leu Gln Leu Pro Glu Ala Cys Ser Glu Ile Lys His Glu Ala	
445 450 455	
ttt aag aat cat gtg ttc aat gta gac aat gca aaa ttt gta gtt ata	1506
Phe Lys Asn His Val Phe Asn Val Asp Asn Ala Lys Phe Val Val Ile	
460 465 470	
ttt gac ctc agt gcc ctg act aca att gga aat gcc aaa aac tca cta	1554
Phe Asp Leu Ser Ala Leu Thr Thr Ile Gly Asn Ala Lys Asn Ser Leu	
475 480 485	
ata ggg atg tgg gcg cta tct cca act gtc ttt gca ctt ctg agt aag	1602
Ile Gly Met Trp Ala Leu Ser Pro Thr Val Phe Ala Leu Leu Ser Lys	
490 495 500	
aat ctg atg att gtg cac agt gac ctg gct gtt cac ttc cct gcc att	1650
Asn Leu Met Ile Val His Ser Asp Leu Ala Val His Phe Pro Ala Ile	
505 510 515 520	
cag tat gct gtg ctc tac aca ttg tat tct cat tgt acc agg cat gat	1698
Gln Tyr Ala Val Leu Tyr Thr Leu Tyr Ser His Cys Thr Arg His Asp	
525 530 535	

cac ttt atc tct agt agc ctc agt tct tcc tct cct tct ttg ttt gat	1746
His Phe Ile Ser Ser Ser Leu Ser Ser Ser Ser Pro Ser Leu Phe Asp	
540 545 550	
gga gct gtg att agc act gta act acg gct aca aag aaa cat ttc tca	1794
Gly Ala Val Ile Ser Thr Val Thr Thr Ala Thr Lys Lys His Phe Ser	
555 560 565	
att ata tta aat ctt ctg gga ata tta ctt aag aaa gat aac ctt aac	1842
Ile Ile Leu Asn Leu Leu Gly Ile Leu Leu Lys Lys Asp Asn Leu Asn	
570 575 580	
cag gac acg agg aaa ctg tta atg act tgg gct ttg gaa gca gct gtt	1890
Gln Asp Thr Arg Lys Leu Leu Met Thr Trp Ala Leu Glu Ala Ala Val	
585 590 595 600	
tta atg aag aag tct gaa aca tac gca cct tta ttc tct ctt ccg tct	1938
Leu Met Lys Lys Ser Glu Thr Tyr Ala Pro Leu Phe Ser Leu Pro Ser	
605 610 615	
ttc cat aaa ttt tgc aaa ggc ctt tta gcc aac act ctc gtt gaa gat	1986
Phe His Lys Phe Cys Lys Gly Leu Leu Ala Asn Thr Leu Val Glu Asp	
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gtg aat atc tgt ctg cag gca tgc agc agt cta cat gct ctg tcc tct	2034
Val Asn Ile Cys Leu Gln Ala Cys Ser Ser Leu His Ala Leu Ser Ser	
635 640 645	
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Ser Leu Pro Asp Asp Leu Leu Gln Arg Cys Val Asp Val Cys Arg Val	
650 655 660	
caa cta gtg cac agt gga act cgt att cga caa gca ttt gga aaa ctg	2130
Gln Leu Val His Ser Gly Thr Arg Ile Arg Gln Ala Phe Gly Lys Leu	
665 670 675 680	
ttg aaa tca att cct tta gat gtt gtc cta agc aat aac aat cac aca	2178
Leu Lys Ser Ile Pro Leu Asp Val Val Leu Ser Asn Asn Asn His Thr	
685 690 695	
gaa att caa gaa att tct tta gca tta aga agt cac atg agt aaa gca	2226
Glu Ile Gln Glu Ile Ser Leu Ala Leu Arg Ser His Met Ser Lys Ala	
700 705 710	
cca agt aat aca ttc cac ccc caa gat ttc tct gat gtt att agt ttt	2274
Pro Ser Asn Thr Phe His Pro Gln Asp Phe Ser Asp Val Ile Ser Phe	
715 720 725	
att ttg tat ggg aac tct cat aga aca ggg aag gac aat tgg ttg gaa	2322
Ile Leu Tyr Gly Asn Ser His Arg Thr Gly Lys Asp Asn Trp Leu Glu	
730 735 740	
aga ctg ttc tat agc tgc cag aga ctg gat aag cgt gac cag tca aca	2370
Arg Leu Phe Tyr Ser Cys Gln Arg Leu Asp Lys Arg Asp Gln Ser Thr	

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Ile Pro Arg Asn Leu Leu Lys Thr Asp Ala Val Leu Trp Gln Trp Ala				
	765	770	775	
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Ile Trp Glu Ala Ala Gln Phe Thr Val Leu Ser Lys Leu Arg Thr Pro				
	780	785	790	
ctg ggc aga gct caa gac acc ttc cag aca att gaa ggt atc att cga				2514
Leu Gly Arg Ala Gln Asp Thr Phe Gln Thr Ile Glu Gly Ile Ile Arg				
	795	800	805	
agt ctc gca gct cac aca tta aac cct gat cag gat gtt agt cag tgg				2562
Ser Leu Ala Ala His Thr Leu Asn Pro Asp Gln Asp Val Ser Gln Trp				
	810	815	820	
aca act gca gac aat gat gaa ggc cat ggt aac aac caa ctt aga ctt				2610
Thr Thr Ala Asp Asn Asp Glu Gly His Gly Asn Asn Gln Leu Arg Leu				
	825	830	835	840
gtt ctt ctt ctg cag tat ctg gaa aat ctg gag aaa tta atg tat aat				2658
Val Leu Leu Leu Gln Tyr Leu Glu Asn Leu Glu Lys Leu Met Tyr Asn				
	845	850	855	
gca tac gag gga tgt gct aat gca tta act tca cct ccc aag gtc att				2706
Ala Tyr Glu Gly Cys Ala Asn Ala Leu Thr Ser Pro Pro Lys Val Ile				
	860	865	870	
aga act ttt ttc tat acc aat cgc caa act tgt cag gac tgg cta acg				2754
Arg Thr Phe Phe Tyr Thr Asn Arg Gln Thr Cys Gln Asp Trp Leu Thr				
	875	880	885	
cgg att cga ctc tcc atc atg agg gta gga ttg ttg gca ggc cag cct				2802
Arg Ile Arg Leu Ser Ile Met Arg Val Gly Leu Leu Ala Gly Gln Pro				
	890	895	900	
gca gtg aca gtg aga cat ggc ttt gac ttg ctt aca gag atg aaa aca				2850
Ala Val Thr Val Arg His Gly Phe Asp Leu Leu Thr Glu Met Lys Thr				
	905	910	915	920
acc agc cta tct cag ggg aat gaa ttg gaa gta acc att atg atg gtg				2898
Thr Ser Leu Ser Gln Gly Asn Glu Leu Glu Val Thr Ile Met Met Val				
	925	930	935	
gta gaa gca tta tgt gaa ctt cat tgt cct gaa gct ata cag gga att				2946
Val Glu Ala Leu Cys Glu Leu His Cys Pro Glu Ala Ile Gln Gly Ile				
	940	945	950	
gct gtc tgg tca tca tct att gtt gga aaa aat ctt ctg tgg att aac				2994
Ala Val Trp Ser Ser Ser Ile Val Gly Lys Asn Leu Leu Trp Ile Asn				
	955	960	965	
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Ser Val Ala Gln Gln Ala Glu Gly Arg Phe Glu Lys Ala Ser Val Glu
 970 975 980

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 Tyr Gln Glu His Leu Cys Ala Met Thr Gly Val Asp Cys Cys Ile Ser
 985 990 995 1000

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 Ser Phe Asp Lys Ser Val Leu Thr Leu Ala Asn Ala Gly Arg Asn Ser
 1005 1010 1015

gcc agc ccg aaa cat tct ctg aat ggt gaa tcc aga aaa act gtg ctg 3186
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 1035 1040 1045

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 1065 1070 1075 1080

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 Ser Leu Asn Leu Lys Ala Asp Phe Asn Tyr Ile Lys Ser Leu Ser Ser
 1085 1090 1095

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 1100 1105 1110

cca gga gaa aat atc aat cta ctt gct gga gga tca aaa gaa aaa ata 3474
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 1115 1120 1125

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 Asp Met Lys Lys Leu Leu Pro Asn Met Leu Ser Pro Asp Pro Arg Glu
 1130 1135 1140

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 1145 1150 1155 1160

gca act gct tta aac ccg ata gaa caa gat cag aag tgg cag tct ata 3618
 Ala Thr Ala Leu Asn Pro Ile Glu Gln Asp Gln Lys Trp Gln Ser Ile
 1165 1170 1175

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 1180 1185 1190

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Gly Pro Leu Arg Leu Ser Thr Leu Thr Val Ser Gln Ser Leu Pro Val	
1195 1200 1205	
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Ser Asn Arg Leu Ser Thr Glu Asp Cys Leu Ile Pro Leu Phe Ser Glu	
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Leu Arg Tyr Thr Met Tyr Gln Asn Gln Leu Leu Glu Lys Ile Lys Glu	
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Gln Thr Val Pro Ile Arg Ser His Leu Met Glu Leu Gly Leu Thr Ala	
1275 1280 1285	
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Ala Lys Phe Ala Arg Lys Arg Gly Asn Val Ser Leu Ala Thr Arg Leu	
1290 1295 1300	
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Asp Leu Val Gln His Phe Lys Lys Leu Ser Thr Gln Gly Gln Val Asp	
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Glu Lys Trp Gly Pro Glu Leu Asp Ile Glu Lys Thr Lys Leu Leu Tyr	
1340 1345 1350	
aca gca ggc cag tca aca cat gca atg gaa atg ttg agt tct tgt gcc	4194
Thr Ala Gly Gln Ser Thr His Ala Met Glu Met Leu Ser Ser Cys Ala	
1355 1360 1365	
ata tct ttc tgc aag tct gtg aaa gct gaa tat gca gtt gct aaa tca	4242
Ile Ser Phe Cys Lys Ser Val Lys Ala Glu Tyr Ala Val Ala Lys Ser	
1370 1375 1380	
att ctg aca ctg gct aaa tgg atc cag gca gaa tgg aaa gag att tca	4290
Ile Leu Thr Leu Ala Lys Trp Ile Gln Ala Glu Trp Lys Glu Ile Ser	
1385 1390 1395 1400	
gga cag ctg aaa cag gtt tac aga gct cag cac caa cag aac ttc aca	4338
Gly Gln Leu Lys Gln Val Tyr Arg Ala Gln His Gln Gln Asn Phe Thr	
1405 1410 1415	

ggt ctt tct act ttg tct aaa aac ata ctc act cta ata gaa ctg cca 4386
 Gly Leu Ser Thr Leu Ser Lys Asn Ile Leu Thr Leu Ile Glu Leu Pro
 1420 1425 1430

tct gtt aat acg atg gaa gaa gag tat cct cgg atc gag agt gaa tct 4434
 Ser Val Asn Thr Met Glu Glu Glu Tyr Pro Arg Ile Glu Ser Glu Ser
 1435 1440 1445

aca gtg cat att gga gtt gga gaa cct gac ttc att ttg gga cag ttg 4482
 Thr Val His Ile Gly Val Gly Glu Pro Asp Phe Ile Leu Gly Gln Leu
 1450 1455 1460

tat cac ctg tct tca gta cag gca cct gaa gta gcc aaa tct tgg gca 4530
 Tyr His Leu Ser Ser Val Gln Ala Pro Glu Val Ala Lys Ser Trp Ala
 1465 1470 1475 1480

gcg ttg gcc agc tgg gct tat agg tgg ggc aga aag gtg gtt gac aat 4578
 Ala Leu Ala Ser Trp Ala Tyr Arg Trp Gly Arg Lys Val Val Asp Asn
 1485 1490 1495

gcc agt cag gga gaa ggt gtt cgt ctg ctg cct aga gaa aaa tct gaa 4626
 Ala Ser Gln Gly Glu Gly Val Arg Leu Leu Pro Arg Glu Lys Ser Glu
 1500 1505 1510

gtt cag aat cta ctt cca gac act ata act gag gaa gag aaa gag aga 4674
 Val Gln Asn Leu Leu Pro Asp Thr Ile Thr Glu Glu Glu Lys Glu Arg
 1515 1520 1525

ata tat ggt att ctt gga cag gct gtg tgt cgg ccg gcg ggg att cag 4722
 Ile Tyr Gly Ile Leu Gly Gln Ala Val Cys Arg Pro Ala Gly Ile Gln
 1530 1535 1540

gat gaa gat ata aca ctt cag ata act gag agt gaa gac aac gaa gaa 4770
 Asp Glu Asp Ile Thr Leu Gln Ile Thr Glu Ser Glu Asp Asn Glu Glu
 1545 1550 1555 1560

gat gac atg gtt gat gtt atc tgg cgt cag ttg ata tca agc tgc cca 4818
 Asp Asp Met Val Asp Val Ile Trp Arg Gln Leu Ile Ser Ser Cys Pro
 1565 1570 1575

tgg ctt tca gaa ctt gat gaa agt gca act gaa gga gtt att aaa gtg 4866
 Trp Leu Ser Glu Leu Asp Glu Ser Ala Thr Glu Gly Val Ile Lys Val
 1580 1585 1590

tgg agg aaa gtt gta gat aga ata ttc agc ctg tac aaa ctc tct tgc 4914
 Trp Arg Lys Val Val Asp Arg Ile Phe Ser Leu Tyr Lys Leu Ser Cys
 1595 1600 1605

agt gca tac ttt act ttc ctt aaa ctc aac gct ggt caa att cct tta 4962
 Ser Ala Tyr Phe Thr Phe Leu Lys Leu Asn Ala Gly Gln Ile Pro Leu
 1610 1615 1620

gat gag gat gac cct agg ctg cat tta agt cac aga gtg gaa cag agc 5010
 Asp Glu Asp Asp Pro Arg Leu His Leu Ser His Arg Val Glu Gln Ser

1625	1630	1635	1640	
act gat gac atg att gtg atg gcc aca ttg cgc ctg ctg cgg ttg ctc				5058
Thr Asp Asp Met Ile Val Met Ala Thr Leu Arg Leu Leu Arg Leu Leu				
	1645	1650	1655	
gtg aag cat gct ggt gag ctt cgg cag tat ctg gag cac ggc ttg gag				5106
Val Lys His Ala Gly Glu Leu Arg Gln Tyr Leu Glu His Gly Leu Glu				
	1660	1665	1670	
aca aca ccc act gca cca tgg aga gga att att ccg caa ctt ttc tca				5154
Thr Thr Pro Thr Ala Pro Trp Arg Gly Ile Ile Pro Gln Leu Phe Ser				
	1675	1680	1685	
cgc tta aac cac cct gaa gtg tat gtg cgc caa agt att tgt aac ctt				5202
Arg Leu Asn His Pro Glu Val Tyr Val Arg Gln Ser Ile Cys Asn Leu				
	1690	1695	1700	
ctc tgc cgt gtg gct caa gat tcc cca cat ctc ata ttg tat cct gca				5250
Leu Cys Arg Val Ala Gln Asp Ser Pro His Leu Ile Leu Tyr Pro Ala				
	1705	1710	1715	1720
ata gtg ggt acc ata tcg ctt agt agt gaa tcc cag gct tca gga aat				5298
Ile Val Gly Thr Ile Ser Leu Ser Ser Glu Ser Gln Ala Ser Gly Asn				
	1725	1730	1735	
aaa ttt tcc act gca att cca act tta ctt ggc aat att caa gga gaa				5346
Lys Phe Ser Thr Ala Ile Pro Thr Leu Leu Gly Asn Ile Gln Gly Glu				
	1740	1745	1750	
gaa ttg ctg gtt tct gaa tgt gag gga gga agt cct cct gca tct cag				5394
Glu Leu Leu Val Ser Glu Cys Glu Gly Gly Ser Pro Pro Ala Ser Gln				
	1755	1760	1765	
gat agc aat aag gat gaa cct aaa agt gga tta aat gaa gac caa gcc				5442
Asp Ser Asn Lys Asp Glu Pro Lys Ser Gly Leu Asn Glu Asp Gln Ala				
	1770	1775	1780	
atg atg cag gat tgt tac agc aaa att gta gat aag ctg tcc tct gca				5490
Met Met Gln Asp Cys Tyr Ser Lys Ile Val Asp Lys Leu Ser Ser Ala				
	1785	1790	1795	1800
aac ccc acc atg gta tta cag gtt cag atg ctc gtg gct gaa ctg cgc				5538
Asn Pro Thr Met Val Leu Gln Val Gln Met Leu Val Ala Glu Leu Arg				
	1805	1810	1815	
agg gtc act gtg ctc tgg gat gag ctc tgg ctg gga gtt ttg ctg caa				5586
Arg Val Thr Val Leu Trp Asp Glu Leu Trp Leu Gly Val Leu Leu Gln				
	1820	1825	1830	
caa cac atg tat gtc ctg aga cga att cag cag ctt gaa gat gag gtg				5634
Gln His Met Tyr Val Leu Arg Arg Ile Gln Gln Leu Glu Asp Glu Val				
	1835	1840	1845	
aag aga gtc cag aac aac aac acc tta cgc aaa gaa gag aaa att gca				5682

Lys	Arg	Val	Gln	Asn	Asn	Asn	Thr	Leu	Arg	Lys	Glu	Glu	Lys	Ile	Ala		
1850							1855				1860						
atc	atg	agg	gag	aag	cac	aca	gct	ttg	atg	aag	ccc	atc	gta	ttt	gct	5730	
Ile	Met	Arg	Glu	Lys	His	Thr	Ala	Leu	Met	Lys	Pro	Ile	Val	Phe	Ala		
1865					1870					1875					1880		
ttg	gag	cat	gtg	agg	agt	atc	aca	gcg	gct	cct	gca	gaa	aca	cct	cat	5778	
Leu	Glu	His	Val	Arg	Ser	Ile	Thr	Ala	Ala	Pro	Ala	Glu	Thr	Pro	His		
				1885					1890					1895			
gaa	aaa	tgg	ttt	cag	gat	aac	tat	ggg	gat	gcc	att	gaa	aat	gcc	cta	5826	
Glu	Lys	Trp	Phe	Gln	Asp	Asn	Tyr	Gly	Asp	Ala	Ile	Glu	Asn	Ala	Leu		
			1900					1905					1910				
gaa	aaa	ctg	aag	act	cca	ttg	aac	cct	gca	aag	cct	ggg	agc	agc	tgg	5874	
Glu	Lys	Leu	Lys	Thr	Pro	Leu	Asn	Pro	Ala	Lys	Pro	Gly	Ser	Ser	Trp		
		1915					1920					1925					
att	cca	ttt	aaa	gag	ata	atg	cta	agt	ttg	caa	cag	aga	gca	cag	aaa	5922	
Ile	Pro	Phe	Lys	Glu	Ile	Met	Leu	Ser	Leu	Gln	Gln	Arg	Ala	Gln	Lys		
	1930					1935					1940						
cgt	gca	agt	tac	atc	ttg	cgt	ctt	gaa	gaa	atc	agt	cca	tgg	ttg	gct	5970	
Arg	Ala	Ser	Tyr	Ile	Leu	Arg	Leu	Glu	Glu	Ile	Ser	Pro	Trp	Leu	Ala		
1945					1950					1955					1960		
gcc	atg	act	aac	act	gaa	att	gct	ctt	cct	ggg	gaa	gtc	tca	gcc	aga	6018	
Ala	Met	Thr	Asn	Thr	Glu	Ile	Ala	Leu	Pro	Gly	Glu	Val	Ser	Ala	Arg		
			1965						1970				1975				
gac	act	gtc	aca	atc	cat	agt	gtg	ggc	gga	acc	atc	aca	atc	tta	ccg	6066	
Asp	Thr	Val	Thr	Ile	His	Ser	Val	Gly	Gly	Thr	Ile	Thr	Ile	Leu	Pro		
		1980						1985					1990				
act	aaa	acc	aag	cca	aag	aaa	ctt	ctc	ttt	ctt	gga	tca	gat	ggg	aag	6114	
Thr	Lys	Thr	Lys	Pro	Lys	Lys	Leu	Leu	Phe	Leu	Gly	Ser	Asp	Gly	Lys		
		1995					2000					2005					
agc	tat	cct	tat	ctt	ttc	aaa	gga	ctg	gag	gat	tta	cat	ctg	gat	gag	6162	
Ser	Tyr	Pro	Tyr	Leu	Phe	Lys	Gly	Leu	Glu	Asp	Leu	His	Leu	Asp	Glu		
	2010					2015					2020						
aga	ata	atg	cag	ttc	cta	tct	att	gtg	aat	acc	atg	ttt	gct	aca	att	6210	
Arg	Ile	Met	Gln	Phe	Leu	Ser	Ile	Val	Asn	Thr	Met	Phe	Ala	Thr	Ile		
2025					2030					2035					2040		
aat	cgc	caa	gaa	aca	ccc	cgg	ttc	cat	gct	cga	cac	tat	tct	gta	aca	6258	
Asn	Arg	Gln	Glu	Thr	Pro	Arg	Phe	His	Ala	Arg	His	Tyr	Ser	Val	Thr		
				2045					2050					2055			
cca	cta	gga	aca	aga	tca	gga	cta	atc	cag	tgg	gta	gat	gga	gcc	aca	6306	
Pro	Leu	Gly	Thr	Arg	Ser	Gly	Leu	Ile	Gln	Trp	Val	Asp	Gly	Ala	Thr		
			2060					2065					2070				

ccc tta ttt ggt ctt tac aaa cga tgg caa caa cgg gaa gct gcc tta	6354
Pro Leu Phe Gly Leu Tyr Lys Arg Trp Gln Gln Arg Glu Ala Ala Leu	
2075 2080 2085	
caa gca caa aag gcc caa gat tcc tac caa act cct cag aat cct gga	6402
Gln Ala Gln Lys Ala Gln Asp Ser Tyr Gln Thr Pro Gln Asn Pro Gly	
2090 2095 2100	
att gta ccc cgt cct agt gaa ctt tat tac agt aaa att ggc cct gct	6450
Ile Val Pro Arg Pro Ser Glu Leu Tyr Tyr Ser Lys Ile Gly Pro Ala	
2105 2110 2115 2120	
ttg aaa aca gtt ggg ctt agc ctg gat gtg tcc cgt cgg gat tgg cct	6498
Leu Lys Thr Val Gly Leu Ser Leu Asp Val Ser Arg Arg Asp Trp Pro	
2125 2130 2135	
ctt cat gta atg aag gca gta ttg gaa gag tta atg gag gcc aca ccc	6546
Leu His Val Met Lys Ala Val Leu Glu Glu Leu Met Glu Ala Thr Pro	
2140 2145 2150	
ccg aat ctc ctt gcc aaa gag ctc tgg tca tct tgc aca aca cct gat	6594
Pro Asn Leu Leu Ala Lys Glu Leu Trp Ser Ser Cys Thr Thr Pro Asp	
2155 2160 2165	
gaa tgg tgg aga gtt acg cag tct tat gca aga tct act gca gtc atg	6642
Glu Trp Trp Arg Val Thr Gln Ser Tyr Ala Arg Ser Thr Ala Val Met	
2170 2175 2180	
tct atg gtt gga tac ata att ggc ctt gga gac aga cat ctg gat aat	6690
Ser Met Val Gly Tyr Ile Ile Gly Leu Gly Asp Arg His Leu Asp Asn	
2185 2190 2195 2200	
gtt ctt ata gat atg acg act gga gaa gtt gtt cac ata gat tac aat	6738
Val Leu Ile Asp Met Thr Thr Gly Glu Val Val His Ile Asp Tyr Asn	
2205 2210 2215	
gtt tgc ttt gaa aaa ggt aaa agc ctt aga gtt cct gag aaa gta cct	6786
Val Cys Phe Glu Lys Gly Lys Ser Leu Arg Val Pro Glu Lys Val Pro	
2220 2225 2230	
ttt cga atg aca caa aac att gaa aca gca ctg ggt gta act gga gta	6834
Phe Arg Met Thr Gln Asn Ile Glu Thr Ala Leu Gly Val Thr Gly Val	
2235 2240 2245	
gaa ggt gta ttt agg ctt tca tgt gag cag gtt tta cac att atg cgg	6882
Glu Gly Val Phe Arg Leu Ser Cys Glu Gln Val Leu His Ile Met Arg	
2250 2255 2260	
cgt ggc aga gag acc ctg ctg acg ctg ctg gag gcc ttt gtg tac gac	6930
Arg Gly Arg Glu Thr Leu Leu Thr Leu Leu Glu Ala Phe Val Tyr Asp	
2265 2270 2275 2280	
cct ctg gtg gac tgg aca gca gga ggc gag gct ggg ttt gct ggt gct	6978
Pro Leu Val Asp Trp Thr Ala Gly Gly Glu Ala Gly Phe Ala Gly Ala	
2285 2290 2295	

gtc tat ggt gga ggt ggc cag cag gcc gag agc aag cag agc aag aga	7026
Val Tyr Gly Gly Gly Gly Gln Gln Ala Glu Ser Lys Gln Ser Lys Arg	
2300 2305 2310	
gag atg gag cga gag atc acc cgc agc ctg ttt tct tct aga gta gct	7074
Glu Met Glu Arg Glu Ile Thr Arg Ser Leu Phe Ser Ser Arg Val Ala	
2315 2320 2325	
gag att aag gtg aac tgg ttt aag aat aga gat gag atg ctg gtt gtg	7122
Glu Ile Lys Val Asn Trp Phe Lys Asn Arg Asp Glu Met Leu Val Val	
2330 2335 2340	
ctt ccc aag ttg gac ggt agc tta gat gaa tac cta agc ttg caa gag	7170
Leu Pro Lys Leu Asp Gly Ser Leu Asp Glu Tyr Leu Ser Leu Gln Glu	
2345 2350 2355 2360	
caa ctg aca gat gtg gaa aaa ctg cag ggc aaa cta ctg gag gaa ata	7218
Gln Leu Thr Asp Val Glu Lys Leu Gln Gly Lys Leu Leu Glu Glu Ile	
2365 2370 2375	
gag ttt cta gaa gga gct gaa ggg gtg gat cat cct tct cat act ctg	7266
Glu Phe Leu Glu Gly Ala Glu Gly Val Asp His Pro Ser His Thr Leu	
2380 2385 2390	
caa cac agg tat tct gag cac acc caa cta cag act cag caa aga gct	7314
Gln His Arg Tyr Ser Glu His Thr Gln Leu Gln Thr Gln Gln Arg Ala	
2395 2400 2405	
gtt cag gaa gca atc cag gtg aag ctg aat gaa ttt gaa caa tgg ata	7362
Val Gln Glu Ala Ile Gln Val Lys Leu Asn Glu Phe Glu Gln Trp Ile	
2410 2415 2420	
aca cat tat cag gct gca ttc aat aat tta gaa gca aca cag ctt gca	7410
Thr His Tyr Gln Ala Ala Phe Asn Asn Leu Glu Ala Thr Gln Leu Ala	
2425 2430 2435 2440	
agc ttg ctt caa gag ata agc aca caa atg gac ctt ggt cct cca agt	7458
Ser Leu Leu Gln Glu Ile Ser Thr Gln Met Asp Leu Gly Pro Pro Ser	
2445 2450 2455	
tac gtg cca gca aca gcc ttt ctg cag aat gct ggt cag gcc cac ttg	7506
Tyr Val Pro Ala Thr Ala Phe Leu Gln Asn Ala Gly Gln Ala His Leu	
2460 2465 2470	
att agc cag tgc gag cag ctg gag ggg gag gtt ggt gct ctc ctg cag	7554
Ile Ser Gln Cys Glu Gln Leu Glu Gly Glu Val Gly Ala Leu Leu Gln	
2475 2480 2485	
cag agg cgc tcc gtg ctc cgt ggc tgt ctg gag caa ctg cat cac tat	7602
Gln Arg Arg Ser Val Leu Arg Gly Cys Leu Glu Gln Leu His His Tyr	
2490 2495 2500	
gca acc gtg gcc ctg cag tat ccg aag gcc ata ttt cag aaa cat cga	7650
Ala Thr Val Ala Leu Gln Tyr Pro Lys Ala Ile Phe Gln Lys His Arg	

2505	2510	2515	2520	
att gaa cag tgg aag acc tgg atg gaa gag ctc atc tgt aac acc aca				7698
Ile Glu Gln Trp Lys Thr Trp Met Glu Glu Leu Ile Cys Asn Thr Thr				
	2525	2530	2535	
gta gag cgt tgt caa gag ctc tat agg aaa tat gaa atg caa tat gct				7746
Val Glu Arg Cys Gln Glu Leu Tyr Arg Lys Tyr Glu Met Gln Tyr Ala				
	2540	2545	2550	
ccc cag cca ccc cca aca gtg tgt cag ttc atc act gcc act gaa atg				7794
Pro Gln Pro Pro Pro Thr Val Cys Gln Phe Ile Thr Ala Thr Glu Met				
	2555	2560	2565	
acc ctg cag cga tac gca gca gac atc aac agc aga ctt att aga caa				7842
Thr Leu Gln Arg Tyr Ala Ala Asp Ile Asn Ser Arg Leu Ile Arg Gln				
	2570	2575	2580	
gtg gaa cgc ttg aaa cag gaa gct gtc act gtg cca gtt tgt gaa gat				7890
Val Glu Arg Leu Lys Gln Glu Ala Val Thr Val Pro Val Cys Glu Asp				
	2585	2590	2595	2600
cag ttg aaa gaa att gaa cgt tgc att aaa gtt ttc ctt cat gag aat				7938
Gln Leu Lys Glu Ile Glu Arg Cys Ile Lys Val Phe Leu His Glu Asn				
	2605	2610	2615	
gga gaa gaa gga tct ttg agt cta gca agt gtt att att tct gcc ctt				7986
Gly Glu Glu Gly Ser Leu Ser Leu Ala Ser Val Ile Ile Ser Ala Leu				
	2620	2625	2630	
tgt acc ctt aca agg cgt aac ctg atg atg gaa ggt gca gcg tca agt				8034
Cys Thr Leu Thr Arg Arg Asn Leu Met Met Glu Gly Ala Ala Ser Ser				
	2635	2640	2645	
gct gga gaa cag ctg gtt gat ctg act tct cgg gat gga gcc tgg ttc				8082
Ala Gly Glu Gln Leu Val Asp Leu Thr Ser Arg Asp Gly Ala Trp Phe				
	2650	2655	2660	
ttg gag gaa ctc tgc agt atg agc gga aac gtc acc tgc ttg gtt cag				8130
Leu Glu Glu Leu Cys Ser Met Ser Gly Asn Val Thr Cys Leu Val Gln				
	2665	2670	2675	2680
tta ctg aag cag tgc cac ctg gtg cca cag gac tta gat atc ccg aac				8178
Leu Leu Lys Gln Cys His Leu Val Pro Gln Asp Leu Asp Ile Pro Asn				
	2685	2690	2695	
ccc atg gaa gcg tct gag aca gtt cac tta gcc aat gga gtg tat acc				8226
Pro Met Glu Ala Ser Glu Thr Val His Leu Ala Asn Gly Val Tyr Thr				
	2700	2705	2710	
tca ctt cag gaa ttg aat tcg aat ttc cgg caa atc ata ttt cca gaa				8274
Ser Leu Gln Glu Leu Asn Ser Asn Phe Arg Gln Ile Ile Phe Pro Glu				
	2715	2720	2725	
gca ctt cga tgt tta atg aaa ggg gaa tac acg tta gaa agt atg ctg				8322

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ctc ttg ata ggg cta ccc aac caa gcc ctc gga ctc	aca ctg tgc agt	8994
Leu Leu Ile Gly Leu Pro Asn Gln Ala Leu Gly Leu Thr Leu Cys Ser		
2955	2960	2965
ttt atc agt gct ctg ggt gta gac atc att gct caa gta gag gca aag		9042
Phe Ile Ser Ala Leu Gly Val Asp Ile Ile Ala Gln Val Glu Ala Lys		
2970	2975	2980
gac ttt ggt gcc gaa agc aaa gtt tct gtt gat gat ctc tgt aag aaa		9090
Asp Phe Gly Ala Glu Ser Lys Val Ser Val Asp Asp Leu Cys Lys Lys		
2985	2990	3000
gcg gtg gaa cat aac atc cag ata ggg aag ttc tct cag ctg gtt atg		9138
Ala Val Glu His Asn Ile Gln Ile Gly Lys Phe Ser Gln Leu Val Met		
3005	3010	3015
aac agg gca act gtg tta gca agt tct tac gac act gcc tgg aag aag		9186
Asn Arg Ala Thr Val Leu Ala Ser Ser Tyr Asp Thr Ala Trp Lys Lys		
3020	3025	3030
cat gac ttg gtg cga agg cta gaa acc agt att tct tct tgt aag aca		9234
His Asp Leu Val Arg Arg Leu Glu Thr Ser Ile Ser Ser Cys Lys Thr		
3035	3040	3045
agc ctg cag cgg gtt cag ctg cat att gcc atg ttt cag tgg caa cat		9282
Ser Leu Gln Arg Val Gln Leu His Ile Ala Met Phe Gln Trp Gln His		
3050	3055	3060
gaa gat cta ctt atc aat aga cca caa gcc atg tca gtc aca cct ccc		9330
Glu Asp Leu Leu Ile Asn Arg Pro Gln Ala Met Ser Val Thr Pro Pro		
3065	3070	3080
cca cgg tct gct atc cta acc agc atg aaa aag aag ctg cat acc ctg		9378
Pro Arg Ser Ala Ile Leu Thr Ser Met Lys Lys Lys Leu His Thr Leu		
3085	3090	3095
agc cag att gaa act tct att gca aca gtt cag gag aag cta gct gca		9426
Ser Gln Ile Glu Thr Ser Ile Ala Thr Val Gln Glu Lys Leu Ala Ala		
3100	3105	3110
ctt gaa tca agt att gaa cag cga ctc aag tgg gca ggt ggt gcc aac		9474
Leu Glu Ser Ser Ile Glu Gln Arg Leu Lys Trp Ala Gly Gly Ala Asn		
3115	3120	3125
cct gca ttg gcc cct gta cta caa gat ttt gaa gca acg ata gct gaa		9522
Pro Ala Leu Ala Pro Val Leu Gln Asp Phe Glu Ala Thr Ile Ala Glu		
3130	3135	3140
aga aga aat ctt gtc ctt aaa gag agc caa aga gca agt cag gtc aca		9570
Arg Arg Asn Leu Val Leu Lys Glu Ser Gln Arg Ala Ser Gln Val Thr		
3145	3150	3160
ttt ctc tgc agc aat atc att cat ttt gaa agt tta cga aca aga act		9618
Phe Leu Cys Ser Asn Ile Ile His Phe Glu Ser Leu Arg Thr Arg Thr		
3165	3170	3175

gca gaa gcc tta aac ctg gat gcg gcg tta ttt gaa cta atc aag cga	9666
Ala Glu Ala Leu Asn Leu Asp Ala Ala Leu Phe Glu Leu Ile Lys Arg	
3180 3185 3190	
tgt cag cag atg tgt tcg ttt gca tca cag ttt aac agt tca gtg tct	9714
Cys Gln Gln Met Cys Ser Phe Ala Ser Gln Phe Asn Ser Ser Val Ser	
3195 3200 3205	
gag tta gag ctt cgt tta tta cag aga gtg gac act ggt ctt gaa cat	9762
Glu Leu Glu Leu Arg Leu Leu Gln Arg Val Asp Thr Gly Leu Glu His	
3210 3215 3220	
cct att ggc agc tct gaa tgg ctt ttg tca gca cac aaa cag ttg acc	9810
Pro Ile Gly Ser Ser Glu Trp Leu Leu Ser Ala His Lys Gln Leu Thr	
3225 3230 3235 3240	
cag gat atg tct act cag agg gca att cag aca gag aaa gag cag cag	9858
Gln Asp Met Ser Thr Gln Arg Ala Ile Gln Thr Glu Lys Glu Gln Gln	
3245 3250 3255	
ata gaa acg gtc tgt gaa aca att cag aat ctg gtt gat aat ata aag	9906
Ile Glu Thr Val Cys Glu Thr Ile Gln Asn Leu Val Asp Asn Ile Lys	
3260 3265 3270	
act gtg ctc act ggt cat aac cga cag ctt gga gat gtc aaa cat ctc	9954
Thr Val Leu Thr Gly His Asn Arg Gln Leu Gly Asp Val Lys His Leu	
3275 3280 3285	
ttg aaa gct atg gct aag gat gaa gaa gct gct ctg gca gat ggt gaa	10002
Leu Lys Ala Met Ala Lys Asp Glu Glu Ala Ala Leu Ala Asp Gly Glu	
3290 3295 3300	
gat gtt ccc tat gag aac agt gtt agg cag ttt ttg ggt gaa tat aaa	10050
Asp Val Pro Tyr Glu Asn Ser Val Arg Gln Phe Leu Gly Glu Tyr Lys	
3305 3310 3315 3320	
tca tgg caa gac aac att caa aca gtt cta ttt aca tta gtc cag gct	10098
Ser Trp Gln Asp Asn Ile Gln Thr Val Leu Phe Thr Leu Val Gln Ala	
3325 3330 3335	
atg ggt cag gtt cga agt caa gaa cac gtt gaa atg ctc cag gaa atc	10146
Met Gly Gln Val Arg Ser Gln Glu His Val Glu Met Leu Gln Glu Ile	
3340 3345 3350	
act ccc acc ttg aaa gaa ctg aaa aca caa agt cag agt atc tat aat	10194
Thr Pro Thr Leu Lys Glu Leu Lys Thr Gln Ser Gln Ser Ile Tyr Asn	
3355 3360 3365	
aat tta gtg agt ttt gca tca ccc tta gtc acc gat gca aca aat gaa	10242
Asn Leu Val Ser Phe Ala Ser Pro Leu Val Thr Asp Ala Thr Asn Glu	
3370 3375 3380	
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Cys Ser Ser Pro Thr Ser Ser Ala Thr Tyr Gln Pro Ser Phe Ala Ala	

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Gln Asn Ala Arg Lys Leu Ile Gln Lys Asn Leu Ala Thr Ser Ala Asp			
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Thr Pro Pro Ser Thr Val Pro Gly Thr Gly Lys Ser Val Ala Cys Ser			
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Pro Lys Lys Ala Val Arg Asp Pro Lys Thr Gly Lys Ala Val Gln Glu			
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Arg Asn Ser Tyr Ala Val Ser Val Trp Lys Arg Val Lys Ala Lys Leu			
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Val Asp Tyr Val Ile Lys Glu Ala Thr Asn Leu Asp Asn Leu Ala Gln			
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Leu Tyr Glu Gly Trp Thr Ala Trp Val *			
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<211> 3521

<212> PRT

<213> Homo sapiens

<400> 2

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      20              25              30
Lys Glu Phe Ile Gln Gln Pro Glu Asn Lys Leu Val Leu Val Lys Gln
      35              40              45
Leu Asp Asn Ile Leu Ala Ala Val His Asp Val Leu Asn Glu Ser Ser
      50              55              60
Lys Leu Leu Gln Glu Leu Arg Gln Glu Gly Ala Cys Cys Leu Gly Leu
      65              70              75              80
Leu Cys Ala Ser Leu Ser Tyr Glu Ala Glu Lys Ile Phe Lys Trp Ile
      85              90              95
Phe Ser Lys Phe Ser Ser Ser Ala Lys Asp Glu Val Lys Leu Leu Tyr
      100             105             110
Leu Cys Ala Thr Tyr Lys Ala Leu Glu Thr Val Gly Glu Lys Lys Ala
      115             120             125
Phe Ser Ser Val Met Gln Leu Val Met Thr Ser Leu Gln Ser Ile Leu
      130             135             140
Glu Asn Val Asp Thr Pro Glu Leu Leu Cys Lys Cys Val Lys Cys Ile
      145             150             155             160
Leu Leu Val Ala Arg Cys Tyr Pro His Ile Phe Ser Thr Asn Phe Arg
      165             170             175
Asp Thr Val Asp Ile Leu Val Gly Trp His Ile Asp His Thr Gln Lys
      180             185             190
Pro Ser Leu Thr Gln Gln Val Ser Gly Trp Leu Gln Ser Leu Glu Pro
      195             200             205
Phe Trp Val Ala Asp Leu Ala Phe Ser Thr Thr Leu Leu Gly Gln Phe
      210             215             220
Leu Glu Asp Met Glu Ala Tyr Ala Glu Asp Leu Ser His Val Ala Ser
      225             230             235             240
Gly Glu Ser Val Asp Glu Asp Val Pro Pro Pro Ser Val Ser Leu Pro
      245             250             255
Lys Leu Ala Ala Leu Leu Arg Val Phe Ser Thr Val Val Arg Ser Ile
      260             265             270
Gly Glu Arg Phe Ser Pro Ile Arg Gly Pro Pro Ile Thr Glu Ala Tyr
      275             280             285
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Gln Val Phe Phe Ser Glu Ala Val Leu Thr Ala Ala Asn Glu Cys Val

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Glu	Gln	Ile	Asn	Thr	Lys	Leu	Pro	Ser	Ser	Phe	Val	Glu	Lys	Leu	Phe
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Ile	Pro	Ser	Ser	Lys	Leu	Leu	Phe	Leu	Arg	Tyr	His	Lys	Glu	Lys	Glu
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Val	Val	Ala	Val	Ala	His	Ala	Val	Tyr	Gln	Ala	Val	Leu	Ser	Leu	Lys
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Asn	Ile	Pro	Val	Leu	Glu	Thr	Ala	Tyr	Lys	Leu	Ile	Leu	Gly	Glu	Met
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Thr	Cys	Ala	Leu	Asn	Asn	Leu	Leu	His	Ser	Leu	Gln	Leu	Pro	Glu	Ala
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Cys	Ser	Glu	Ile	Lys	His	Glu	Ala	Phe	Lys	Asn	His	Val	Phe	Asn	Val
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Asp	Asn	Ala	Lys	Phe	Val	Val	Ile	Phe	Asp	Leu	Ser	Ala	Leu	Thr	Thr
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Ile	Gly	Asn	Ala	Lys	Asn	Ser	Leu	Ile	Gly	Met	Trp	Ala	Leu	Ser	Pro
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Thr	Val	Phe	Ala	Leu	Leu	Ser	Lys	Asn	Leu	Met	Ile	Val	His	Ser	Asp
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Leu	Ala	Val	His	Phe	Pro	Ala	Ile	Gln	Tyr	Ala	Val	Leu	Tyr	Thr	Leu
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Tyr	Ser	His	Cys	Thr	Arg	His	Asp	His	Phe	Ile	Ser	Ser	Ser	Leu	Ser
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Ser	Ser	Ser	Pro	Ser	Leu	Phe	Asp	Gly	Ala	Val	Ile	Ser	Thr	Val	Thr
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Thr	Ala	Thr	Lys	Lys	His	Phe	Ser	Ile	Ile	Leu	Asn	Leu	Leu	Gly	Ile
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Leu	Leu	Lys	Lys	Asp	Asn	Leu	Asn	Gln	Asp	Thr	Arg	Lys	Leu	Leu	Met
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Thr	Trp	Ala	Leu	Glu	Ala	Ala	Val	Leu	Met	Lys	Lys	Ser	Glu	Thr	Tyr
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Ala	Pro	Leu	Phe	Ser	Leu	Pro	Ser	Phe	His	Lys	Phe	Cys	Lys	Gly	Leu
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Leu	Ala	Asn	Thr	Leu	Val	Glu	Asp	Val	Asn	Ile	Cys	Leu	Gln	Ala	Cys
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Ser	Ser	Leu	His	Ala	Leu	Ser	Ser	Ser	Leu	Pro	Asp	Asp	Leu	Leu	Gln
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Arg	Cys	Val	Asp	Val	Cys	Arg	Val	Gln	Leu	Val	His	Ser	Gly	Thr	Arg
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Ile	Arg	Gln	Ala	Phe	Gly	Lys	Leu	Leu	Lys	Ser	Ile	Pro	Leu	Asp	Val
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Gln Thr Ile Glu Gly Ile Ile Arg Ser Leu Ala Ala His Thr Leu Asn
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Cys Thr Glu Gln Leu Glu Leu Leu Pro Gly Glu Asn Ile Asn Leu Leu
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Ser Ser Ala Leu	Glu Asn Thr Val	Ser Asn Arg Leu	Ser Thr Glu Asp		
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Cys Leu Ile Pro	Leu Phe Ser Glu	Ala Leu Arg Ser	Cys Lys Gln His		
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Asp Val Arg Pro	Trp Met Gln Ala	Leu Arg Tyr Thr	Met Tyr Gln Asn		
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Gln Leu Leu Glu	Lys Ile Lys Glu	Gln Thr Val Pro	Ile Arg Ser His		
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Leu Met Glu Leu	Gly Leu Thr Ala	Ala Lys Phe Ala	Arg Lys Arg Gly		
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Asn Val Ser Leu	Ala Thr Arg Leu	Leu Leu Ala Gln	Cys Ser Glu Val	Gln	
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Leu Gly Lys Thr	Thr Thr Ala Gln	Asp Leu Val Gln	His Phe Lys Lys		
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Leu Ser Thr Gln	Gly Gln Val Asp	Glu Lys Trp Gly	Pro Glu Leu Asp		
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Ile Glu Lys Thr	Lys Leu Leu Tyr	Thr Ala Gly Gln	Ser Thr His Ala		
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Met Glu Met Leu	Ser Ser Cys Ala	Ile Ser Phe Cys	Lys Ser Val Lys		
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Gln Ala Glu Trp	Lys Glu Ile Ser	Gly Gln Leu Lys	Gln Val Tyr Arg		
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Pro Glu Val Ala	Lys Ser Trp Ala	Ala Leu Ala Ser	Trp Ala Tyr Arg		
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Trp Gly Arg Lys	Val Val Asp Asn	Ala Ser Gln Gly	Glu Gly Val Arg		
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Arg Gln Leu Ile	Ser Ser Cys Pro	Trp Leu Ser Glu	Leu Asp Glu Ser		
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Ala Thr Glu Gly	Val Ile Lys Val	Trp Arg Lys Val	Val Val Asp Arg	Ile	
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Leu Asn Ala Gly	Gln Ile Pro Leu	Asp Glu Asp Asp	Pro Arg Leu His		
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Gly	Asp	Ala	Ile	Glu	Asn	Ala	Leu	Glu	Lys	Leu	Lys	Thr	Pro	Leu	Asn	
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Pro	Ala	Lys	Pro	Gly	Ser	Ser	Trp	Ile	Pro	Phe	Lys	Glu	Ile	Met	Leu	
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Ser	Leu	Gln	Gln	Arg	Ala	Gln	Lys	Arg	Ala	Ser	Tyr	Ile	Leu	Arg	Leu	
1940				1945				1950								
Glu	Glu	Ile	Ser	Pro	Trp	Leu	Ala	Ala	Met	Thr	Asn	Thr	Glu	Ile	Ala	
1955				1960				1965								
Leu	Pro	Gly	Glu	Val	Ser	Ala	Arg	Asp	Thr	Val	Thr	Ile	His	Ser	Val	
1970				1975				1980								
Gly	Gly	Thr	Ile	Thr	Ile	Leu	Pro	Thr	Lys	Thr	Lys	Pro	Lys	Lys	Leu	
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Leu	Phe	Leu	Gly	Ser	Asp	Gly	Lys	Ser	Tyr	Pro	Tyr	Leu	Phe	Lys	Gly	
2005				2010				2015								
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Val	Asn	Thr	Met	Phe	Ala	Thr	Ile	Asn	Arg	Gln	Glu	Thr	Pro	Arg	Phe	
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His	Ala	Arg	His	Tyr	Ser	Val	Thr	Pro	Leu	Gly	Thr	Arg	Ser	Gly	Leu	
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Ile	Gln	Trp	Val	Asp	Gly	Ala	Thr	Pro	Leu	Phe	Gly	Leu	Tyr	Lys	Arg	

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Ser Leu Phe Ser	Ser Arg Val Ala	Glu Ile Lys Val	Asn Trp Phe Lys
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Asp Glu Tyr Leu	Ser Leu Gln Glu	Gln Leu Thr Asp	Val Glu Lys Leu
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Gln Gly Lys Leu	Leu Glu Glu Ile	Glu Phe Leu Glu	Gly Ala Glu Gly
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Val Asp His Pro	Ser His Thr Leu	Gln His Arg Tyr	Ser Glu His Thr
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Gln Leu Gln Thr	Gln Gln Arg Ala	Val Gln Glu Ala	Ile Gln Val Lys
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Leu Asn Glu Phe	Glu Gln Trp Ile	Thr His Tyr Gln	Ala Ala Phe Asn
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Asn Leu Glu Ala	Thr Gln Leu Ala	Ser Leu Leu Gln	Glu Ile Ser Thr
2435	2440	2445	
Gln Met Asp Leu	Gly Pro Pro Ser	Tyr Val Pro Ala	Thr Ala Phe Leu
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Gln Asn Ala Gly	Gln Ala His Leu	Ile Ser Gln Cys	Glu Gln Leu Glu
2465	2470	2475	2480
Gly Glu Val Gly	Ala Leu Leu Gln	Gln Arg Arg Ser	Val Leu Arg Gly
2485	2490	2495	
Cys Leu Glu Gln	Leu His His Tyr	Ala Thr Val Ala	Leu Gln Tyr Pro
2500	2505	2510	

Lys Ala Ile Phe Gln Lys His Arg Ile Glu Gln Trp Lys Thr Trp Met
 2515 2520 2525
 Glu Glu Leu Ile Cys Asn Thr Thr Val Glu Arg Cys Gln Glu Leu Tyr
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 Arg Lys Tyr Glu Met Gln Tyr Ala Pro Gln Pro Pro Pro Thr Val Cys
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 Gln Phe Ile Thr Ala Thr Glu Met Thr Leu Gln Arg Tyr Ala Ala Asp
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 Val Thr Val Pro Val Cys Glu Asp Gln Leu Lys Glu Ile Glu Arg Cys
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 Ile Lys Val Phe Leu His Glu Asn Gly Glu Glu Gly Ser Leu Ser Leu
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 Ala Ser Val Ile Ile Ser Ala Leu Cys Thr Leu Thr Arg Arg Asn Leu
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 Met Met Glu Gly Ala Ala Ser Ser Ala Gly Glu Gln Leu Val Asp Leu
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 Thr Ser Arg Asp Gly Ala Trp Phe Leu Glu Glu Leu Cys Ser Met Ser
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 Gly Asn Val Thr Cys Leu Val Gln Leu Leu Lys Gln Cys His Leu Val
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 Pro Gln Asp Leu Asp Ile Pro Asn Pro Met Glu Ala Ser Glu Thr Val
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 His Leu Ala Asn Gly Val Tyr Thr Ser Leu Gln Glu Leu Asn Ser Asn
 2705 2710 2715 2720
 Phe Arg Gln Ile Ile Phe Pro Glu Ala Leu Arg Cys Leu Met Lys Gly
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 Glu Tyr Thr Leu Glu Ser Met Leu His Glu Leu Asp Gly Leu Ile Glu
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 Gln Thr Thr Asp Gly Val Pro Leu Gln Thr Leu Val Glu Ser Leu Gln
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 His Tyr Ile Asp Val Ala Arg Leu Leu His Ala Gln Tyr Gly Glu Leu
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 2885 2890 2895
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 Phe Thr Ala Asp Phe Val Arg Gln Leu Leu Ile Gly Leu Pro Asn Gln

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Ile Ile Ala Gln Val Glu Ala Lys Asp Phe Gly Ala Glu Ser Lys Val			
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Ser Val Asp Asp Leu Cys Lys Lys Ala Val Glu His Asn Ile Gln Ile			
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Gly Lys Phe Ser Gln Leu Val Met Asn Arg Ala Thr Val Leu Ala Ser			
	3010	3015	3020
Ser Tyr Asp Thr Ala Trp Lys Lys His Asp Leu Val Arg Arg Leu Glu			
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Thr Ser Ile Ser Ser Cys Lys Thr Ser Leu Gln Arg Val Gln Leu His			
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Gln Ala Met Ser Val Thr Pro Pro Pro Arg Ser Ala Ile Leu Thr Ser			
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Met Lys Lys Lys Leu His Thr Leu Ser Gln Ile Glu Thr Ser Ile Ala			
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Thr Val Gln Glu Lys Leu Ala Ala Leu Glu Ser Ser Ile Glu Gln Arg			
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Leu Lys Trp Ala Gly Gly Ala Asn Pro Ala Leu Ala Pro Val Leu Gln			
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Asp Phe Glu Ala Thr Ile Ala Glu Arg Arg Asn Leu Val Leu Lys Glu			
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Ser Gln Arg Ala Ser Gln Val Thr Phe Leu Cys Ser Asn Ile Ile His			
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Phe Glu Ser Leu Arg Thr Arg Thr Ala Glu Ala Leu Asn Leu Asp Ala			
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Ala Leu Phe Glu Leu Ile Lys Arg Cys Gln Gln Met Cys Ser Phe Ala			
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Ser Gln Phe Asn Ser Ser Val Ser Glu Leu Glu Leu Arg Leu Leu Gln			
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Arg Val Asp Thr Gly Leu Glu His Pro Ile Gly Ser Ser Glu Trp Leu			
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Leu Ser Ala His Lys Gln Leu Thr Gln Asp Met Ser Thr Gln Arg Ala			
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Ile Gln Thr Glu Lys Glu Gln Gln Ile Glu Thr Val Cys Glu Thr Ile			
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Gln Asn Leu Val Asp Asn Ile Lys Thr Val Leu Thr Gly His Asn Arg			
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Glu Ala Ala Leu Ala Asp Gly Glu Asp Val Pro Tyr Glu Asn Ser Val			
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Val Leu Phe Thr Leu Val Gln Ala Met Gly Gln Val Arg Ser Gln Glu			
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His Val Glu Met Leu Gln Glu Ile Thr Pro Thr Leu Lys Glu Leu Lys			
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Thr Gln Ser Gln Ser Ile Tyr Asn Asn Leu Val Ser Phe Ala Ser Pro			
	3365	3370	3375
Leu Val Thr Asp Ala Thr Asn Glu Cys Ser Ser Pro Thr Ser Ser Ala			
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Thr Tyr Gln Pro Ser Phe Ala Ala Ala Val Arg Ser Asn Thr Gly Gln
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Lys Thr Gln Pro Asp Val Met Ser Gln Asn Ala Arg Lys Leu Ile Gln
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3425 3430 3435 3440
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3460 3465 3470
Trp Lys Arg Val Lys Ala Lys Leu Glu Gly Arg Asp Val Asp Pro Asn
3475 3480 3485
Arg Arg Met Ser Val Ala Glu Gln Val Asp Tyr Val Ile Lys Glu Ala
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gggtcactgc c atg gag gag ccg cag tca gat cct agc gtc gag ccc cct 290
          Met Glu Glu Pro Gln Ser Asp Pro Ser Val Glu Pro Pro
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ctg agt cag gaa aca ttt tca gac cta tgg aaa cta ctt cct gaa aac 338
Leu Ser Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro Glu Asn
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Asn Val Leu Ser Pro Leu Pro Ser Gln Ala Met Asp Asp Leu Met Leu
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tcc ccg gac gat att gaa caa tgg ttc act gaa gac cca ggt cca gat 434
Ser Pro Asp Asp Ile Glu Gln Trp Phe Thr Glu Asp Pro Gly Pro Asp
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gaa gct ccc aga atg cca gag gct gct ccc cgc gtg gcc cct gca cca 482
Glu Ala Pro Arg Met Pro Glu Ala Ala Pro Arg Val Ala Pro Ala Pro
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gca gct cct aca ccg gcg gcc cct gca cca gcc ccc tcc tgg ccc ctg 530

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Ala	Ala	Pro	Thr	Pro	Ala	Ala	Pro	Ala	Pro	Ala	Pro	Ser	Trp	Pro	Leu		
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Ser	Ser	Ser	Val	Pro	Ser	Gln	Lys	Thr	Tyr	Gln	Gly	Ser	Tyr	Gly	Phe		
	95					100					105						
cgt	ctg	ggc	ttc	ttg	cat	tct	ggg	aca	gcc	aag	tct	gtg	act	tgc	acg	626	
Arg	Leu	Gly	Phe	Leu	His	Ser	Gly	Thr	Ala	Lys	Ser	Val	Thr	Cys	Thr		
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tac	tcc	cct	gcc	ctc	aac	aag	atg	ttt	tgc	caa	ctg	gcc	aag	acc	tgc	674	
Tyr	Ser	Pro	Ala	Leu	Asn	Lys	Met	Phe	Cys	Gln	Leu	Ala	Lys	Thr	Cys		
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cct	gtg	cag	ctg	tgg	gtt	gat	tcc	aca	ccc	ccg	ccc	ggc	acc	cgc	gtc	722	
Pro	Val	Gln	Leu	Trp	Val	Asp	Ser	Thr	Pro	Pro	Pro	Gly	Thr	Arg	Val		
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cgc	gcc	atg	gcc	atc	tac	aag	cag	tca	cag	cac	atg	acg	gag	gtt	gtg	770	
Arg	Ala	Met	Ala	Ile	Tyr	Lys	Gln	Ser	Gln	His	Met	Thr	Glu	Val	Val		
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Arg	Arg	Cys	Pro	His	His	Glu	Arg	Cys	Ser	Asp	Ser	Asp	Gly	Leu	Ala		
	175					180					185						
cct	cct	cag	cat	ctt	atc	cga	gtg	gaa	gga	aat	ttg	cgt	gtg	gag	tat	866	
Pro	Pro	Gln	His	Leu	Ile	Arg	Val	Glu	Gly	Asn	Leu	Arg	Val	Glu	Tyr		
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ccg	cct	gag	gtt	ggc	tct	gac	tgt	acc	acc	atc	cac	tac	aac	tac	atg	962	
Pro	Pro	Glu	Val	Gly	Ser	Asp	Cys	Thr	Thr	Ile	His	Tyr	Asn	Tyr	Met		
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Cys	Asn	Ser	Ser	Cys	Met	Gly	Gly	Met	Asn	Arg	Arg	Pro	Ile	Leu	Thr		
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atc	atc	aca	ctg	gaa	gac	tcc	agt	ggt	aat	cta	ctg	gga	cgg	aac	agc	1058	
Ile	Ile	Thr	Leu	Glu	Asp	Ser	Ser	Gly	Asn	Leu	Leu	Gly	Arg	Asn	Ser		
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Phe	Glu	Val	Arg	Val	Cys	Ala	Cys	Pro	Gly	Arg	Asp	Arg	Arg	Thr	Glu		
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Glu	Glu	Asn	Leu	Arg	Lys	Lys	Gly	Glu	Pro	His	His	Glu	Leu	Pro	Pro		
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cca aag aag aaa cca ctg gat gga gaa tat ttc acc ctt cag atc cgt 1250
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 320 325 330

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ctc aag gat gcc cag gct ggg aag gag cca ggg ggg agc agg gct cac 1346
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 370 375 380

aaa ctc atg ttc aag aca gaa ggg cct gac tca gac tga cattctccac 1443
 Lys Leu Met Phe Lys Thr Glu Gly Pro Asp Ser Asp *
 385 390

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Ser Pro Leu Pro Ser Gln Ala Met Asp Asp Leu Met Leu Ser Pro Asp
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Asp Ile Glu Gln Trp Phe Thr Glu Asp Pro Gly Pro Asp Glu Ala Pro
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Thr Pro Ala Ala Pro Ala Pro Ala Pro Ser Trp Pro Leu Ser Ser Ser
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Val Pro Ser Gln Lys Thr Tyr Gln Gly Ser Tyr Gly Phe Arg Leu Gly
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Phe Leu His Ser Gly Thr Ala Lys Ser Val Thr Cys Thr Tyr Ser Pro
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Ala Leu Asn Lys Met Phe Cys Gln Leu Ala Lys Thr Cys Pro Val Gln
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Pro His His Glu Arg Cys Ser Asp Ser Asp Gly Leu Ala Pro Pro Gln
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His Leu Ile Arg Val Glu Gly Asn Leu Arg Val Glu Tyr Leu Asp Asp
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Arg Asn Thr Phe Arg His Ser Val Val Val Pro Tyr Glu Pro Pro Glu
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Val Gly Ser Asp Cys Thr Thr Ile His Tyr Asn Tyr Met Cys Asn Ser
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Ser Cys Met Gly Gly Met Asn Arg Arg Pro Ile Leu Thr Ile Ile Thr
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Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Ser Pro Gln Pro Lys Lys
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Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu
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Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp
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Met Trp Ala Leu Ser Pro Thr Val Phe Ala
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ctt ctg agt aag aat ctg atg att gtg cac agt gac ctg gct gtt cac 1780
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15 20 25

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ttc cct gcc att cag tat gct gtg ctc tac aca ttg tat tct cat tgt 1828
Phe Pro Ala Ile Gln Tyr Ala Val Leu Tyr Thr Leu Tyr Ser His Cys
30 35 40

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acc agg cat gat cac ttt atc tct agt agc ctc agt tct tcc tct cct 1876
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45 50 55

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Ser Leu Phe Asp Gly Ala Val Ile Ser Thr Val Thr Thr Ala Thr Lys
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Lys His Phe Ser Ile Ile Leu Asn Leu Leu Gly Ile Leu Leu Lys Lys
75 80 85 90

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gaa gca gct gtt tta atg aag aag tct gaa aca tac gca cct tta ttc	2068
Glu Ala Ala Val Leu Met Lys Lys Ser Glu Thr Tyr Ala Pro Leu Phe	
110 115 120	
tct ctt ccg tct ttc cat aaa ttt tgc aaa ggc ctt tta gcc aac act	2116
Ser Leu Pro Ser Phe His Lys Phe Cys Lys Gly Leu Leu Ala Asn Thr	
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ctc gtt gaa gat gtg aat atc tgt ctg cag gca tgc agc agt cta cat	2164
Leu Val Glu Asp Val Asn Ile Cys Leu Gln Ala Cys Ser Ser Leu His	
140 145 150	
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Ala Leu Ser Ser Ser Leu Pro Asp Asp Leu Leu Gln Arg Cys Val Asp	
155 160 165 170	
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Val Cys Arg Val Gln Leu Val His Ser Gly Thr Arg Ile Arg Gln Ala	
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Phe Gly Lys Leu Leu Lys Ser Ile Pro Leu Asp Val Val Leu Ser Asn	
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Asn Asn His Thr Glu Ile Gln Glu Ile Ser Leu Ala Leu Arg Ser His	
205 210 215	
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220 225 230	
gtt att agt ttt att ttg tat ggg aac tct cat aga aca ggg aag gac	2452
Val Ile Ser Phe Ile Leu Tyr Gly Asn Ser His Arg Thr Gly Lys Asp	
235 240 245 250	
aat tgg ttg gaa aga ctg ttc tat agc tgc cag aga ctg gat aag cgt	2500
Asn Trp Leu Glu Arg Leu Phe Tyr Ser Cys Gln Arg Leu Asp Lys Arg	
255 260 265	
gac cag tca aca att cca cgc aat ctc ctg aag aca gat gct gtc ctt	2548
Asp Gln Ser Thr Ile Pro Arg Asn Leu Leu Lys Thr Asp Ala Val Leu	
270 275 280	
tgg cag tgg gcc ata tgg gaa gct gca caa ttc act gtt ctt tct aag	2596
Trp Gln Trp Ala Ile Trp Glu Ala Ala Gln Phe Thr Val Leu Ser Lys	
285 290 295	
ctg aga acc cca ctg ggc aga gct caa gac acc ttc cag aca att gaa	2644
Leu Arg Thr Pro Leu Gly Arg Ala Gln Asp Thr Phe Gln Thr Ile Glu	
300 305 310	

ggt atc att cga agt ctc gca gct cac aca tta aac cct gat cag gat	2692
Gly Ile Ile Arg Ser Leu Ala Ala His Thr Leu Asn Pro Asp Gln Asp	
315 320 325 330	
ggt agt cag tgg aca act gca gac aat gat gaa ggc cat ggt aac aac	2740
Val Ser Gln Trp Thr Thr Ala Asp Asn Asp Glu Gly His Gly Asn Asn	
335 340 345	
caa ctt aga ctt gtt ctt ctt ctg cag tat ctg gaa aat ctg gag aaa	2788
Gln Leu Arg Leu Val Leu Leu Leu Gln Tyr Leu Glu Asn Leu Glu Lys	
350 355 360	
tta atg tat aat gca tac gag gga tgt gct aat gca tta act tca cct	2836
Leu Met Tyr Asn Ala Tyr Glu Gly Cys Ala Asn Ala Leu Thr Ser Pro	
365 370 375	
ccc aag gtc att aga act ttt ttc tat acc aat cgc caa act tgt cag	2884
Pro Lys Val Ile Arg Thr Phe Phe Tyr Thr Asn Arg Gln Thr Cys Gln	
380 385 390	
gac tgg cta acg cgg att cga ctc tcc atc atg agg gta gga ttg ttg	2932
Asp Trp Leu Thr Arg Ile Arg Leu Ser Ile Met Arg Val Gly Leu Leu	
395 400 405 410	
gca ggc cag cct gca gtg aca gtg aga cat ggc ttt gac ttg ctt aca	2980
Ala Gly Gln Pro Ala Val Thr Val Arg His Gly Phe Asp Leu Leu Thr	
415 420 425	
gag atg aaa aca acc agc cta tct cag ggg aat gaa ttg gaa gta acc	3028
Glu Met Lys Thr Thr Ser Leu Ser Gln Gly Asn Glu Leu Glu Val Thr	
430 435 440	
att atg atg gtg gta gaa gca tta tgt gaa ctt cat tgt cct gaa gct	3076
Ile Met Met Val Val Glu Ala Leu Cys Glu Leu His Cys Pro Glu Ala	
445 450 455	
ata cag gga att gct gtc tgg tca tca tct att gtt gga aaa aat ctt	3124
Ile Gln Gly Ile Ala Val Trp Ser Ser Ser Ile Val Gly Lys Asn Leu	
460 465 470	
ctg tgg att aac tca gtg gct caa cag gct gaa ggg agg ttt gaa aag	3172
Leu Trp Ile Asn Ser Val Ala Gln Gln Ala Glu Gly Arg Phe Glu Lys	
475 480 485 490	
gcc tct gtg gag tac cag gaa cac ctg tgt gcc atg aca ggt gtt gat	3220
Ala Ser Val Glu Tyr Gln Glu His Leu Cys Ala Met Thr Gly Val Asp	
495 500 505	
tgc tgc atc tcc agc ttt gac aaa tgc gtg ctc acc tta gcc aat gct	3268
Cys Cys Ile Ser Ser Phe Asp Lys Ser Val Leu Thr Leu Ala Asn Ala	
510 515 520	
ggg cgt aac agt gcc agc ccg aaa cat tct ctg aat ggt gaa tcc aga	3316
Gly Arg Asn Ser Ala Ser Pro Lys His Ser Leu Asn Gly Glu Ser Arg	

525	530	535	
aaa act gtg ctg tcc aaa ccg act gac tct tcc cct gag gtt ata aat			3364
Lys Thr Val Leu Ser Lys Pro Thr Asp Ser Ser Pro Glu Val Ile Asn			
540	545	550	
tat tta gga aat aaa gca tgt gag tgc tac atc tca att gcc gat tgg			3412
Tyr Leu Gly Asn Lys Ala Cys Glu Cys Tyr Ile Ser Ile Ala Asp Trp			
555	560	565	570
gct gct gtg cag gaa tgg cag aac gct atc cat gac ttg aaa aag agt			3460
Ala Ala Val Gln Glu Trp Gln Asn Ala Ile His Asp Leu Lys Lys Ser			
575	580	585	
acc agt agc act tcc ctc aac ctg aaa gct gac ttc aac tat ata aaa			3508
Thr Ser Ser Thr Ser Leu Asn Leu Lys Ala Asp Phe Asn Tyr Ile Lys			
590	595	600	
tca tta agc agc ttt gag tct gga aaa ttt gtt gaa tgt acc gag caa			3556
Ser Leu Ser Ser Phe Glu Ser Gly Lys Phe Val Glu Cys Thr Glu Gln			
605	610	615	
tta gaa ttg tta cca gga gaa aat atc aat cta ctt gct gga gga tca			3604
Leu Glu Leu Leu Pro Gly Glu Asn Ile Asn Leu Leu Ala Gly Gly Ser			
620	625	630	
aaa gaa aaa ata gac atg aaa aaa ctg ctt cct aac atg tta agt ccg			3652
Lys Glu Lys Ile Asp Met Lys Lys Leu Leu Pro Asn Met Leu Ser Pro			
635	640	645	650
gat ccg agg gaa ctt cag aaa tcc att gaa gtt caa ttg tta aga agt			3700
Asp Pro Arg Glu Leu Gln Lys Ser Ile Glu Val Gln Leu Leu Arg Ser			
655	660	665	
tct gtt tgt ttg gca act gct tta aac ccg ata gaa caa gat cag aag			3748
Ser Val Cys Leu Ala Thr Ala Leu Asn Pro Ile Glu Gln Asp Gln Lys			
670	675	680	
tgg cag tct ata act gaa aat gtg gta aag tac ttg aag caa aca tcc			3796
Trp Gln Ser Ile Thr Glu Asn Val Val Lys Tyr Leu Lys Gln Thr Ser			
685	690	695	
cgc atc gct att gga cct ctg aga ctt tct act tta aca gtt tca cag			3844
Arg Ile Ala Ile Gly Pro Leu Arg Leu Ser Thr Leu Thr Val Ser Gln			
700	705	710	
tct ttg cca gtt cta agt acc ttg cag ctg tat tgc tca tct gct ttg			3892
Ser Leu Pro Val Leu Ser Thr Leu Gln Leu Tyr Cys Ser Ser Ala Leu			
715	720	725	730
gag aac aca gtt tct aac aga ctt tca aca gag gac tgt ctt att cca			3940
Glu Asn Thr Val Ser Asn Arg Leu Ser Thr Glu Asp Cys Leu Ile Pro			
735	740	745	
ctc ttc agt gaa gct tta cgt tca tgt aaa cag cat gac gtg agg cca			3988

Leu Phe Ser Glu Ala Leu Arg Ser Cys Lys Gln His Asp Val Arg Pro	
750	755 760
tgg atg cag gca tta agg tat act atg tac cag aat cag ttg ttg gag	4036
Trp Met Gln Ala Leu Arg Tyr Thr Met Tyr Gln Asn Gln Leu Leu Glu	
765	770 775
aaa att aaa gaa caa aca gtc cca att aga agc cat ctc atg gaa tta	4084
Lys Ile Lys Glu Gln Thr Val Pro Ile Arg Ser His Leu Met Glu Leu	
780	785 790
ggg cta aca gca gca aaa ttt gct aga aaa cga ggg aat gtg tcc ctt	4132
Gly Leu Thr Ala Ala Lys Phe Ala Arg Lys Arg Gly Asn Val Ser Leu	
795	800 805 810
gca aca aga ctg ctg gca cag tgc agt gaa gtt cag ctg gga aag acc	4180
Ala Thr Arg Leu Leu Ala Gln Cys Ser Glu Val Gln Leu Gly Lys Thr	
815	820 825
acc act gca cag gat tta gtc caa cat ttt aaa aaa cta tca acc caa	4228
Thr Thr Ala Gln Asp Leu Val Gln His Phe Lys Lys Leu Ser Thr Gln	
830	835 840
ggg caa gtg gat gaa aaa tgg ggg ccc gaa ctt gat att gaa aaa acc	4276
Gly Gln Val Asp Glu Lys Trp Gly Pro Glu Leu Asp Ile Glu Lys Thr	
845	850 855
aaa ttg ctt tat aca gca ggc cag tca aca cat gca atg gaa atg ttg	4324
Lys Leu Leu Tyr Thr Ala Gly Gln Ser Thr His Ala Met Glu Met Leu	
860	865 870
agt tct tgt gcc ata tct ttc tgc aag tct gtg aaa gct gaa tat gca	4372
Ser Ser Cys Ala Ile Ser Phe Cys Lys Ser Val Lys Ala Glu Tyr Ala	
875	880 885 890
gtt gct aaa tca att ctg aca ctg gct aaa tgg atc cag gca gaa tgg	4420
Val Ala Lys Ser Ile Leu Thr Leu Ala Lys Trp Ile Gln Ala Glu Trp	
895	900 905
aaa gag att tca gga cag ctg aaa cag gtt tac aga gct cag cac caa	4468
Lys Glu Ile Ser Gly Gln Leu Lys Gln Val Tyr Arg Ala Gln His Gln	
910	915 920
cag aac ttc aca ggt ctt tct act ttg tct aaa aac ata ctc act cta	4516
Gln Asn Phe Thr Gly Leu Ser Thr Leu Ser Lys Asn Ile Leu Thr Leu	
925	930 935
ata gaa ctg cca tct gtt aat acg atg gaa gaa gag tat cct cgg atc	4564
Ile Glu Leu Pro Ser Val Asn Thr Met Glu Glu Glu Tyr Pro Arg Ile	
940	945 950
gag agt gaa tct aca gtg cat att gga gtt gga gaa cct gac ttc att	4612
Glu Ser Glu Ser Thr Val His Ile Gly Val Gly Glu Pro Asp Phe Ile	
955	960 965 970

ttg gga cag ttg tat cac ctg tct tca gta cag gca cct gaa gta gcc	4660
Leu Gly Gln Leu Tyr His Leu Ser Ser Val Gln Ala Pro Glu Val Ala	
975 980 985	
aaa tct tgg gca gcg ttg gcc agc tgg gct tat agg tgg ggc aga aag	4708
Lys Ser Trp Ala Ala Leu Ala Ser Trp Ala Tyr Arg Trp Gly Arg Lys	
990 995 1000	
gtg gtt gac aat gcc agt cag gga gaa ggt gtt cgt ctg ctg cct aga	4756
Val Val Asp Asn Ala Ser Gln Gly Glu Gly Val Arg Leu Leu Pro Arg	
1005 1010 1015	
gaa aaa tct gaa gtt cag aat cta ctt cca gac act ata act gag gaa	4804
Glu Lys Ser Glu Val Gln Asn Leu Leu Pro Asp Thr Ile Thr Glu Glu	
1020 1025 1030	
gag aaa gag aga ata tat ggt att ctt gga cag gct gtg tgt cgg ccg	4852
Glu Lys Glu Arg Ile Tyr Gly Ile Leu Gly Gln Ala Val Cys Arg Pro	
1035 1040 1045 1050	
gcg ggg att cag gat gaa gat ata acâ ctt cag ata act gag agt gaa	4900
Ala Gly Ile Gln Asp Glu Asp Ile Thr Leu Gln Ile Thr Glu Ser Glu	
1055 1060 1065	
gac aac gaa gaa gat gac atg gtt gat gtt atc tgg cgt cag ttg ata	4948
Asp Asn Glu Glu Asp Asp Met Val Asp Val Ile Trp Arg Gln Leu Ile	
1070 1075 1080	
tca agc tgc cca tgg ctt tca gaa ctt gat gaa agt gca act gaa gga	4996
Ser Ser Cys Pro Trp Leu Ser Glu Leu Asp Glu Ser Ala Thr Glu Gly	
1085 1090 1095	
gtt att aaa gtg tgg agg aaa gtt gta gat aga ata ttc agc ctg tac	5044
Val Ile Lys Val Trp Arg Lys Val Val Asp Arg Ile Phe Ser Leu Tyr	
1100 1105 1110	
aaa ctc tct tgc agt gca tac ttt act ttc ctt aaa ctc aac gct ggt	5092
Lys Leu Ser Cys Ser Ala Tyr Phe Thr Phe Leu Lys Leu Asn Ala Gly	
1115 1120 1125 1130	
caa att cct tta gat gag gat gac cct agg ctg cat tta agt cac aga	5140
Gln Ile Pro Leu Asp Glu Asp Asp Pro Arg Leu His Leu Ser His Arg	
1135 1140 1145	
gtg gaa cag agc act gat gac atg att gtg atg gcc aca ttg cgc ctg	5188
Val Glu Gln Ser Thr Asp Asp Met Ile Val Met Ala Thr Leu Arg Leu	
1150 1155 1160	
ctg cgg ttg ctc gtg aag cat gct ggt gag ctt cgg cag tat ctg gag	5236
Leu Arg Leu Leu Val Lys His Ala Gly Glu Leu Arg Gln Tyr Leu Glu	
1165 1170 1175	
cac ggc ttg gag aca aca ccc act gca cca tgg aga gga att att ccg	5284
His Gly Leu Glu Thr Thr Pro Thr Ala Pro Trp Arg Gly Ile Ile Pro	
1180 1185 1190	

caa ctt ttc tca cgc tta aac cac cct gaa gtg tat gtg cgc caa agt	5332
Gln Leu Phe Ser Arg Leu Asn His Pro Glu Val Tyr Val Arg Gln Ser	
1195 1200 1205 1210	
att tgt aac ctt ctc tgc cgt gtg gct caa gat tcc cca cat ctc ata	5380
Ile Cys Asn Leu Leu Cys Arg Val Ala Gln Asp Ser Pro His Leu Ile	
1215 1220 1225	
ttg tat cct gca ata gtg ggt acc ata tcg ctt agt agt gaa tcc cag	5428
Leu Tyr Pro Ala Ile Val Gly Thr Ile Ser Leu Ser Ser Glu Ser Gln	
1230 1235 1240	
gct tca gga aat aaa ttt tcc act gca att cca act tta ctt ggc aat	5476
Ala Ser Gly Asn Lys Phe Ser Thr Ala Ile Pro Thr Leu Leu Gly Asn	
1245 1250 1255	
att caa gga gaa gaa ttg ctg gtt tct gaa tgt gag gga gga agt cct	5524
Ile Gln Gly Glu Glu Leu Leu Val Ser Glu Cys Glu Gly Gly Ser Pro	
1260 1265 1270	
cct gca tct cag gat agc aat aag gat gaa cct aaa agt gga tta aat	5572
Pro Ala Ser Gln Asp Ser Asn Lys Asp Glu Pro Lys Ser Gly Leu Asn	
1275 1280 1285 1290	
gaa gac caa gcc atg atg cag gat tgt tac agc aaa att gta gat aag	5620
Glu Asp Gln Ala Met Met Gln Asp Cys Tyr Ser Lys Ile Val Asp Lys	
1295 1300 1305	
ctg tcc tct gca aac ccc acc atg gta tta cag gtt cag atg ctc gtg	5668
Leu Ser Ser Ala Asn Pro Thr Met Val Leu Gln Val Gln Met Leu Val	
1310 1315 1320	
gct gaa ctg cgc agg gtc act gtg ctc tgg gat gag ctc tgg ctg gga	5716
Ala Glu Leu Arg Arg Val Thr Val Leu Trp Asp Glu Leu Trp Leu Gly	
1325 1330 1335	
gtt ttg ctg caa caa cac atg tat gtc ctg aga cga att cag cag ctt	5764
Val Leu Leu Gln Gln His Met Tyr Val Leu Arg Arg Ile Gln Gln Leu	
1340 1345 1350	
gaa gat gag gtg aag aga gtc cag aac aac aac acc tta cgc aaa gaa	5812
Glu Asp Glu Val Lys Arg Val Gln Asn Asn Asn Thr Leu Arg Lys Glu	
1355 1360 1365 1370	
gag aaa att gca atc atg agg gag aag cac aca gct ttg atg aag ccc	5860
Glu Lys Ile Ala Ile Met Arg Glu Lys His Thr Ala Leu Met Lys Pro	
1375 1380 1385	
atc gta ttt gct ttg gag cat gtg agg agt atc aca gcg gct cct gca	5908
Ile Val Phe Ala Leu Glu His Val Arg Ser Ile Thr Ala Ala Pro Ala	
1390 1395 1400	
gaa aca cct cat gaa aaa tgg ttt cag gat aac tat ggt gat gcc att	5956
Glu Thr Pro His Glu Lys Trp Phe Gln Asp Asn Tyr Gly Asp Ala Ile	

1405	1410	1415	
gaa aat gcc cta gaa aaa ctg aag act cca ttg aac cct gca aag cct			6004
Glu Asn Ala Leu Glu Lys Leu Lys Thr Pro Leu Asn Pro Ala Lys Pro			
1420	1425	1430	
ggg agc agc tgg att cca ttt aaa gag ata atg cta agt ttg caa cag			6052
Gly Ser Ser Trp Ile Pro Phe Lys Glu Ile Met Leu Ser Leu Gln Gln			
1435	1440	1445	1450
aga gca cag aaa cgt gca agt tac atc ttg cgt ctt gaa gaa atc agt			6100
Arg Ala Gln Lys Arg Ala Ser Tyr Ile Leu Arg Leu Glu Glu Ile Ser			
1455	1460	1465	
cca tgg ttg gct gcc atg act aac act gaa att gct ctt cct ggg gaa			6148
Pro Trp Leu Ala Ala Met Thr Asn Thr Glu Ile Ala Leu Pro Gly Glu			
1470	1475	1480	
gtc tca gcc aga gac act gtc aca atc cat agt gtg ggc gga acc atc			6196
Val Ser Ala Arg Asp Thr Val Thr Ile His Ser Val Gly Gly Thr Ile			
1485	1490	1495	
aca atc tta ccg act aaa acc aag cca aag aaa ctt ctc ttt ctt gga			6244
Thr Ile Leu Pro Thr Lys Thr Lys Pro Lys Lys Leu Leu Phe Leu Gly			
1500	1505	1510	
tca gat ggg aag agc tat cct tat ctt ttc aaa gga ctg gag gat tta			6292
Ser Asp Gly Lys Ser Tyr Pro Tyr Leu Phe Lys Gly Leu Glu Asp Leu			
1515	1520	1525	1530
cat ctg gat gag aga ata atg cag ttc cta tct att gtg aat acc atg			6340
His Leu Asp Glu Arg Ile Met Gln Phe Leu Ser Ile Val Asn Thr Met			
1535	1540	1545	
ttt gct aca att aat cgc caa gaa aca ccc cgg ttc cat gct cga cac			6388
Phe Ala Thr Ile Asn Arg Gln Glu Thr Pro Arg Phe His Ala Arg His			
1550	1555	1560	
tat tct gta aca cca cta gga aca aga tca gga cta atc cag tgg gta			6436
Tyr Ser Val Thr Pro Leu Gly Thr Arg Ser Gly Leu Ile Gln Trp Val			
1565	1570	1575	
gat gga gcc aca ccc tta ttt ggt ctt tac aaa cga tgg caa caa cgg			6484
Asp Gly Ala Thr Pro Leu Phe Gly Leu Tyr Lys Arg Trp Gln Gln Arg			
1580	1585	1590	
gaa gct gcc tta caa gca caa aag gcc caa gat tcc tac caa act cct			6532
Glu Ala Ala Leu Gln Ala Gln Lys Ala Gln Asp Ser Tyr Gln Thr Pro			
1595	1600	1605	1610
cag aat cct gga att gta ccc cgt cct agt gaa ctt tat tac agt aaa			6580
Gln Asn Pro Gly Ile Val Pro Arg Pro Ser Glu Leu Tyr Tyr Ser Lys			
1615	1620	1625	
att ggc cct gct ttg aaa aca gtt ggg ctt agc ctg gat gtg tcc cgt			6628

Ile Gly Pro Ala Leu Lys Thr Val Gly Leu Ser Leu Asp Val Ser Arg	
1630	1635 1640
cgg gat tgg cct ctt cat gta atg aag gca gta ttg gaa gag tta atg	6676
Arg Asp Trp Pro Leu His Val Met Lys Ala Val Leu Glu Glu Leu Met	
1645	1650 1655
gag gcc aca ccc ccg aat ctc ctt gcc aaa gag ctc tgg tca tct tgc	6724
Glu Ala Thr Pro Pro Asn Leu Leu Ala Lys Glu Leu Trp Ser Ser Cys	
1660	1665 1670
aca aca cct gat gaa tgg tgg aga gtt acg cag tct tat gca aga tct	6772
Thr Thr Pro Asp Glu Trp Trp Arg Val Thr Gln Ser Tyr Ala Arg Ser	
1675	1680 1685 1690
act gca gtc atg tct atg gtt gga tac ata att ggc ctt gga gac aga	6820
Thr Ala Val Met Ser Met Val Gly Tyr Ile Ile Gly Leu Gly Asp Arg	
1695	1700 1705
cat ctg gat aat gtt ctt ata gat atg acg act gga gaa gtt gtt cac	6868
His Leu Asp Asn Val Leu Ile Asp Met Thr Thr Gly Glu Val Val His	
1710	1715 1720
ata gat tac aat gtt tgc ttt gaa aaa ggt aaa agc ctt aga gtt cct	6916
Ile Asp Tyr Asn Val Cys Phe Glu Lys Gly Lys Ser Leu Arg Val Pro	
1725	1730 1735
gag aaa gta cct ttt cga atg aca caa aac att gaa aca gca ctg ggt	6964
Glu Lys Val Pro Phe Arg Met Thr Gln Asn Ile Glu Thr Ala Leu Gly	
1740	1745 1750
gta act gga gta gaa ggt gta ttt agg ctt tca tgt gag cag gtt tta	7012
Val Thr Gly Val Glu Gly Val Phe Arg Leu Ser Cys Glu Gln Val Leu	
1755	1760 1765 1770
cac att atg cgg cgt ggc aga gag acc ctg ctg acg ctg ctg gag gcc	7060
His Ile Met Arg Arg Gly Arg Glu Thr Leu Leu Thr Leu Leu Glu Ala	
1775	1780 1785
ttt gtg tac gac cct ctg gtg gac tgg aca gca gga ggc gag gct ggg	7108
Phe Val Tyr Asp Pro Leu Val Asp Trp Thr Ala Gly Gly Glu Ala Gly	
1790	1795 1800
ttt gct ggt gct gtc tat ggt gga ggt ggc cag cag gcc gag agc aag	7156
Phe Ala Gly Ala Val Tyr Gly Gly Gly Gly Gln Gln Ala Glu Ser Lys	
1805	1810 1815
cag agc aag aga gag atg gag cga gag atc acc cgc agc ctg ttt tct	7204
Gln Ser Lys Arg Glu Met Glu Arg Glu Ile Thr Arg Ser Leu Phe Ser	
1820	1825 1830
tct aga gta gct gag att aag gtg aac tgg ttt aag aat aga gat gag	7252
Ser Arg Val Ala Glu Ile Lys Val Asn Trp Phe Lys Asn Arg Asp Glu	
1835	1840 1845 1850

atg ctg gtt gtg ctt ccc aag ttg gac ggt agc ttä gat gaa tac cta	7300
Met Leu Val Val Leu Pro Lys Leu Asp Gly Ser Leu Asp Glu Tyr Leu	
1855 1860 1865	
agc ttg caa gag caa ctg aca gat gtg gaa aaa ctg cag ggc aaa cta	7348
Ser Leu Gln Glu Gln Leu Thr Asp Val Glu Lys Leu Gln Gly Lys Leu	
1870 1875 1880	
ctg gag gaa ata gag ttt cta gaa gga gct gaa ggg gtg gat cat cct	7396
Leu Glu Glu Ile Glu Phe Leu Glu Gly Ala Glu Gly Val Asp His Pro	
1885 1890 1895	
tct cat act ctg caa cac agg tat tct gag cac acc caa cta cag act	7444
Ser His Thr Leu Gln His Arg Tyr Ser Glu His Thr Gln Leu Gln Thr	
1900 1905 1910	
cag caa aga gct gtt cag gaa gca atc cag gtg aag ctg aat gaa ttt	7492
Gln Gln Arg Ala Val Gln Glu Ala Ile Gln Val Lys Leu Asn Glu Phe	
1915 1920 1925 1930	
gaa caa tgg ata aca cat tat cag gct gca ttc aat aat tta gaa gca	7540
Glu Gln Trp Ile Thr His Tyr Gln Ala Ala Phe Asn Asn Leu Glu Ala	
1935 1940 1945	
aca cag ctt gca agc ttg ctt caa gag ata agc aca caa atg gac ctt	7588
Thr Gln Leu Ala Ser Leu Leu Gln Glu Ile Ser Thr Gln Met Asp Leu	
1950 1955 1960	
ggt cct cca agt tac gtg cca gca aca gcc ttt ctg cag aat gct ggt	7636
Gly Pro Pro Ser Tyr Val Pro Ala Thr Ala Phe Leu Gln Asn Ala Gly	
1965 1970 1975	
cag gcc cac ttg att agc cag tgc gag cag ctg gag ggg gag gtt ggt	7684
Gln Ala His Leu Ile Ser Gln Cys Glu Gln Leu Glu Gly Glu Val Gly	
1980 1985 1990	
gct ctc ctg cag cag agg cgc tcc gtg ctc cgt ggc tgt ctg gag caa	7732
Ala Leu Leu Gln Gln Arg Arg Ser Val Leu Arg Gly Cys Leu Glu Gln	
1995 2000 2005 2010	
ctg cat cac tat gca acc gtg gcc ctg cag tat ccg aag gcc ata ttt	7780
Leu His His Tyr Ala Thr Val Ala Leu Gln Tyr Pro Lys Ala Ile Phe	
2015 2020 2025	
cag aaa cat cga att gaa cag tgg aag acc tgg atg gaa gag ctc atc	7828
Gln Lys His Arg Ile Glu Gln Trp Lys Thr Trp Met Glu Glu Leu Ile	
2030 2035 2040	
tgt aac acc aca gta gag cgt tgt caa gag ctc tat agg aaa tat gaa	7876
Cys Asn Thr Thr Val Glu Arg Cys Gln Glu Leu Tyr Arg Lys Tyr Glu	
2045 2050 2055	
atg caa tat gct ccc cag cca ccc cca aca gtg tgt cag ttc atc act	7924
Met Gln Tyr Ala Pro Gln Pro Pro Pro Thr Val Cys Gln Phe Ile Thr	
2060 2065 2070	

gcc act gaa atg acc ctg cag cga tac gca gca gac atc aac agc aga	7972
Ala Thr Glu Met Thr Leu Gln Arg Tyr Ala Ala Asp Ile Asn Ser Arg	
2075	2080 2085 2090
ctt att aga caa gtg gaa cgc ttg aaa cag gaa gct gtc act gtg cca	8020
Leu Ile Arg Gln Val Glu Arg Leu Lys Gln Glu Ala Val Thr Val Pro	
2095	2100 2105
gtt tgt gaa gat cag ttg aaa gaa att gaa cgt tgc att aaa gtt ttc	8068
Val Cys Glu Asp Gln Leu Lys Glu Ile Glu Arg Cys Ile Lys Val Phe	
2110	2115 2120
ctt cat gag aat gga gaa gaa gga tct ttg agt cta gca agt gtt att	8116
Leu His Glu Asn Gly Glu Glu Gly Ser Leu Ser Leu Ala Ser Val Ile	
2125	2130 2135
att tct gcc ctt tgt acc ctt aca agg cgt aac ctg atg atg gaa ggt	8164
Ile Ser Ala Leu Cys Thr Leu Thr Arg Arg Asn Leu Met Met Glu Gly	
2140	2145 2150
gca gcg tca agt gct gga gaa cag ctg gtt gat ctg act tct cgg gat	8212
Ala Ala Ser Ser Ala Gly Glu Gln Leu Val Asp Leu Thr Ser Arg Asp	
2155	2160 2165 2170
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Gly Ala Trp Phe Leu Glu Glu Leu Cys Ser Met Ser Gly Asn Val Thr	
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Ile Phe Pro Glu Ala Leu Arg Cys Leu Met Lys Gly Glu Tyr Thr Leu	
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Ala Val Leu Tyr Thr Leu Tyr Ser His Cys Thr Arg His Asp His Phe
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Ile Ser Ser Ser Leu Ser Ser Ser Ser Pro Ser Leu Phe Asp Gly Ala
          50           55           60
Val Ile Ser Thr Val Thr Thr Ala Thr Lys Lys His Phe Ser Ile Ile
65           70           75           80
Leu Asn Leu Leu Gly Ile Leu Leu Lys Lys Asp Asn Leu Asn Gln Asp
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aag gcc tct gtg gag tac cag gaa cac ctg tgt gcc atg aca ggt gtt	3149
Lys Ala Ser Val Glu Tyr Gln Glu His Leu Cys Ala Met Thr Gly Val	
990 995 1000	
gat tgc tgc atc tcc agc ttt gac aaa tcg gtg ctc acc tta gcc aat	3197
Asp Cys Cys Ile Ser Ser Phe Asp Lys Ser Val Leu Thr Leu Ala Asn	
1005 1010 1015	
gct ggg cgt aac agt gcc agc ccg aaa cat tct ctg aat ggt gaa tcc	3245
Ala Gly Arg Asn Ser Ala Ser Pro Lys His Ser Leu Asn Gly Glu Ser	
1020 1025 1030 1035	
aga aaa act gtg ctg tcc aaa ccg act gac tct tcc cct gag gtt ata	3293
Arg Lys Thr Val Leu Ser Lys Pro Thr Asp Ser Ser Pro Glu Val Ile	

1040	1045	1050	
aat tat tta gga aat aaa gca tgt gag ttc tac atc tca att gcc gat			3341
Asn Tyr Leu Gly Asn Lys Ala Cys Glu Phe Tyr Ile Ser Ile Ala Asp			
1055	1060	1065	
tggttg gct gct gtg cag gaa tgg cag aac gct atc cat gac ttg aaa aag			3389
Trp Ala Ala Val Gln Glu Trp Gln Asn Ala Ile His Asp Leu Lys Lys			
1070	1075	1080	
agt acc agt agc act tcc ctc aac ctg aaa gct gac ttc aac tat ata			3437
Ser Thr Ser Ser Thr Ser Leu Asn Leu Lys Ala Asp Phe Asn Tyr Ile			
1085	1090	1095	
aaa tca tta agc agc ttt gag tct gga aaa ttt gtt gaa tgt acc gag			3485
Lys Ser Leu Ser Ser Phe Glu Ser Gly Lys Phe Val Glu Cys Thr Glu			
1100	1105	1110	1115
cag tta gaa ttg tta cca gga gaa aat atc aat cta ctt gct gga gga			3533
Gln Leu Glu Leu Leu Pro Gly Glu Asn Ile Asn Leu Leu Ala Gly Gly			
1120	1125	1130	
tca aaa gaa aaa ata gac atg aaa aaa ctg ctt cct aac atg tta agt			3581
Ser Lys Glu Lys Ile Asp Met Lys Lys Leu Leu Pro Asn Met Leu Ser			
1135	1140	1145	
ccg gat ccg agg gaa ctt cag aaa tcc att gaa gtt caa ttg tta aga			3629
Pro Asp Pro Arg Glu Leu Gln Lys Ser Ile Glu Val Gln Leu Leu Arg			
1150	1155	1160	
agt tct gtt tgt ttg gca act gct tta aac ccg ata gaa caa gat cag			3677
Ser Ser Val Cys Leu Ala Thr Ala Leu Asn Pro Ile Glu Gln Asp Gln			
1165	1170	1175	
aag tgg cag tct ata act gaa aat gtg gta aag tac ttg aag caa aca			3725
Lys Trp Gln Ser Ile Thr Glu Asn Val Val Lys Tyr Leu Lys Gln Thr			
1180	1185	1190	1195
tcc cgc atc gct att gga cct ctg aga ctt tct act tta aca gtt tca			3773
Ser Arg Ile Ala Ile Gly Pro Leu Arg Leu Ser Thr Leu Thr Val Ser			
1200	1205	1210	
cag tct ttg cca gtt cta agt acc ttg cag ctg tat tgc tca tct gct			3821
Gln Ser Leu Pro Val Leu Ser Thr Leu Gln Leu Tyr Cys Ser Ser Ala			
1215	1220	1225	
ttg gag aac aca gtt tct aac aga ctt tca aca gag gac tgt ctt att			3869
Leu Glu Asn Thr Val Ser Asn Arg Leu Ser Thr Glu Asp Cys Leu Ile			
1230	1235	1240	
cca ctc ttc agt gaa gct tta cgt tca tgt aaa cag cat gac gtg agg			3917
Pro Leu Phe Ser Glu Ala Leu Arg Ser Cys Lys Gln His Asp Val Arg			
1245	1250	1255	
cca tgg atg cag gca tta agg tat act atg tac cag aat cag ttg ttg			3965

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gcc aaa tct tgg gca gcg ttg gcc agc tgg gct tat agg tgg ggc aga	4637
Ala Lys Ser Trp Ala Ala Leu Ala Ser Trp Ala Tyr Arg Trp Gly Arg	
1485 1490 1495	
aag gtg gtt gac aat gcc agt cag gga gaa ggt gtt cgt ctg ctg cct	4685
Lys Val Val Asp Asn Ala Ser Gln Gly Glu Gly Val Arg Leu Leu Pro	
1500 1505 1510 1515	
aga gaa aaa tct gaa gtt cag aat cta ctt cca gac act ata act gag	4733
Arg Glu Lys Ser Glu Val Gln Asn Leu Leu Pro Asp Thr Ile Thr Glu	
1520 1525 1530	
gaa gag aaa gag aga ata tat ggt att ctt gga cag gct gtg tgt cgg	4781
Glu Glu Lys Glu Arg Ile Tyr Gly Ile Leu Gly Gln Ala Val Cys Arg	
1535 1540 1545	
ccg gcg ggg att cag gat gaa gat ata aca ctt cag ata act gag agt	4829
Pro Ala Gly Ile Gln Asp Glu Asp Ile Thr Leu Gln Ile Thr Glu Ser	
1550 1555 1560	
gaa gac aac gaa gaa gat gac atg gtt gat gtt atc tgg cgt cag ttg	4877
Glu Asp Asn Glu Glu Asp Asp Met Val Asp Val Ile Trp Arg Gln Leu	
1565 1570 1575	
ata tca agc tgc cca tgg ctt tca gaa ctt gat gaa agt gca act gaa	4925
Ile Ser Ser Cys Pro Trp Leu Ser Glu Leu Asp Glu Ser Ala Thr Glu	
1580 1585 1590 1595	
gga gtt att aaa gtg tgg agg aaa gtt gta gat aga ata ttc agc ctg	4973
Gly Val Ile Lys Val Trp Arg Lys Val Val Asp Arg Ile Phe Ser Leu	
1600 1605 1610	
tac aaa ctc tct tgc agt gca tac ttt act ttc ctt aaa ctc aac gct	5021
Tyr Lys Leu Ser Cys Ser Ala Tyr Phe Thr Phe Leu Lys Leu Asn Ala	
1615 1620 1625	
ggt caa att cct tta gat gag gat gac cct agg ctg cat tta agt cac	5069
Gly Gln Ile Pro Leu Asp Glu Asp Asp Pro Arg Leu His Leu Ser His	
1630 1635 1640	
aga gtg gaa cag agc act gat gac atg att gtg atg gcc aca ttg cgc	5117
Arg Val Glu Gln Ser Thr Asp Asp Met Ile Val Met Ala Thr Leu Arg	
1645 1650 1655	
ctg ctg cgg ttg ctc gtg aag cat gct ggt gag ctt cgg cag tat ctg	5165
Leu Leu Arg Leu Leu Val Lys His Ala Gly Glu Leu Arg Gln Tyr Leu	
1660 1665 1670 1675	
gag cac ggc ttg gag aca aca ccc act gca cca tgg agg gga att att	5213
Glu His Gly Leu Glu Thr Thr Pro Thr Ala Pro Trp Arg Gly Ile Ile	
1680 1685 1690	
ccg caa ctt ttc tca cgc tta aac cac cct gaa gtg tat gtg cgc caa	5261
Pro Gln Leu Phe Ser Arg Leu Asn His Pro Glu Val Tyr Val Arg Gln	
1695 1700 1705	

agt att tgt aac ctt ctc tgc cgt gtg gct caa gat tcc cca cat ctc	5309
Ser Ile Cys Asn Leu Leu Cys Arg Val Ala Gln Asp Ser Pro His Leu	
1710 1715 1720	
ata ttg tat cct gca ata gtg ggt acc ata tcg ctt agt agt gaa tcc	5357
Ile Leu Tyr Pro Ala Ile Val Gly Thr Ile Ser Leu Ser Ser Glu Ser	
1725 1730 1735	
cag gct tca gga aat aaa ttt tcc act gca att cca act tta ctt ggc	5405
Gln Ala Ser Gly Asn Lys Phe Ser Thr Ala Ile Pro Thr Leu Leu Gly	
1740 1745 1750 1755	
aat att caa gga gaa gaa ttg ctg gtt tct gaa tgt gag gga gga agt	5453
Asn Ile Gln Gly Glu Glu Leu Leu Val Ser Glu Cys Glu Gly Gly Ser	
1760 1765 1770	
cct cct gca tct cag gat agc aat aag gat gaa cct aaa agt gga tta	5501
Pro Pro Ala Ser Gln Asp Ser Asn Lys Asp Glu Pro Lys Ser Gly Leu	
1775 1780 1785	
aat gaa gac caa gcc atg atg cag gat tgt tac agc aaa att gta gat	5549
Asn Glu Asp Gln Ala Met Met Gln Asp Cys Tyr Ser Lys Ile Val Asp	
1790 1795 1800	
aag ctg tcc tct gca aac ccc acc atg gta tta cag gtt cag atg ctc	5597
Lys Leu Ser Ser Ala Asn Pro Thr Met Val Leu Gln Val Gln Met Leu	
1805 1810 1815	
gtg gct gaa ctg cgc agg gtc act gtg ctc tgg gat gag ctc tgg ctg	5645
Val Ala Glu Leu Arg Arg Val Thr Val Leu Trp Asp Glu Leu Trp Leu	
1820 1825 1830 1835	
gga gtt ttg ctg caa caa cac atg tat gtc ctg aga cga att cag cag	5693
Gly Val Leu Leu Gln Gln His Met Tyr Val Leu Arg Arg Ile Gln Gln	
1840 1845 1850	
ctt gaa gat gag gtg aag aga gtc cag aac aac aac acc tta cgc aaa	5741
Leu Glu Asp Glu Val Lys Arg Val Gln Asn Asn Asn Thr Leu Arg Lys	
1855 1860 1865	
gaa gag aaa att gca atc atg agg gag agg cac aca gct ttg atg aag	5789
Glu Glu Lys Ile Ala Ile Met Arg Glu Arg His Thr Ala Leu Met Lys	
1870 1875 1880	
ccc atc gta ttt gct ttg gag cat gtg agg agt atc aca gcg gct cct	5837
Pro Ile Val Phe Ala Leu Glu His Val Arg Ser Ile Thr Ala Ala Pro	
1885 1890 1895	
gca gaa aca cct cat gaa aaa tgg ttt cag gat aac tat ggt gat gcc	5885
Ala Glu Thr Pro His Glu Lys Trp Phe Gln Asp Asn Tyr Gly Asp Ala	
1900 1905 1910 1915	
att gaa aat gcc cta gaa aaa ctg aag act cca ttg aac cct gca aag	5933
Ile Glu Asn Ala Leu Glu Lys Leu Lys Thr Pro Leu Asn Pro Ala Lys	

	1920	1925	1930	
cct ggg agc agc tgg att cca ttt aaa gag ata atg cta agt ttg caa				5981
Pro Gly Ser Ser Trp Ile Pro Phe Lys Glu Ile Met Leu Ser Leu Gln				
	1935	1940	1945	
cag aga gca cag aaa cgt gca agt tac atc ttg cgt ctt gaa gaa atc				6029
Gln Arg Ala Gln Lys Arg Ala Ser Tyr Ile Leu Arg Leu Glu Glu Ile				
	1950	1955	1960	
agt cca tgg ttg gct gcc atg act aac act gaa att gct ctt cct ggg				6077
Ser Pro Trp Leu Ala Ala Met Thr Asn Thr Glu Ile Ala Leu Pro Gly				
	1965	1970	1975	
gaa gtc tca gcc aga gac act gtc aca atc cat agt gtg ggc gga acc				6125
Glu Val Ser Ala Arg Asp Thr Val Thr Ile His Ser Val Gly Gly Thr				
	1980	1985	1990	1995
atc aca atc tta ccg act aaa acc aag cca aag aaa ctt ctc ttt ctt				6173
Ile Thr Ile Leu Pro Thr Lys Thr Lys Pro Lys Lys Leu Leu Phe Leu				
	2000	2005	2010	
gga tca gat ggg aag agc tat cct tat ctt ttc aaa gga ctg gag gat				6221
Gly Ser Asp Gly Lys Ser Tyr Pro Tyr Leu Phe Lys Gly Leu Glu Asp				
	2015	2020	2025	
tta cat ctg gat gag aga ata atg cag ttc cta tct att gtg aat acc				6269
Leu His Leu Asp Glu Arg Ile Met Gln Phe Leu Ser Ile Val Asn Thr				
	2030	2035	2040	
atg ttt gct aca att aat cgc caa gaa aca ccc cgg ttc cat gct cga				6317
Met Phe Ala Thr Ile Asn Arg Gln Glu Thr Pro Arg Phe His Ala Arg				
	2045	2050	2055	
cac tat tct gta aca cca cta gga aca aga tca gga cta atc cag tgg				6365
His Tyr Ser Val Thr Pro Leu Gly Thr Arg Ser Gly Leu Ile Gln Trp				
	2060	2065	2070	2075
gta gat gga gcc aca ccc tta ttt ggt ctt tac aaa cga tgg caa caa				6413
Val Asp Gly Ala Thr Pro Leu Phe Gly Leu Tyr Lys Arg Trp Gln Gln				
	2080	2085	2090	
cgg gaa gct gcc tta caa gca caa aag gcc caa gat tcc tac caa act				6461
Arg Glu Ala Ala Leu Gln Ala Gln Lys Ala Gln Asp Ser Tyr Gln Thr				
	2095	2100	2105	
cct cag aat cct gga att gta ccc cgt cct agt gaa ctt tat tac agt				6509
Pro Gln Asn Pro Gly Ile Val Pro Arg Pro Ser Glu Leu Tyr Tyr Ser				
	2110	2115	2120	
aaa att ggc cct gct ttg aaa aca gtt ggg ctt agc ctg gat gtg tcc				6557
Lys Ile Gly Pro Ala Leu Lys Thr Val Gly Leu Ser Leu Asp Val Ser				
	2125	2130	2135	
cgt cgg gat tgg cct ctt cat gta atg aag gca gta ttg gaa gag tta				6605

Arg Arg Asp Trp Pro Leu His Val Met Lys Ala Val Leu Glu Glu Leu	
2140 2145 2150 2155	
atg gag gcc aca ccc ccg aat ctc ctt gcc aaa gag ctc tgg tca tct	6653
Met Glu Ala Thr Pro Pro Asn Leu Leu Ala Lys Glu Leu Trp Ser Ser	
2160 2165 2170	
tgc aca aca cct gat gaa tgg tgg aga gtt acg cag tct tat gca aga	6701
Cys Thr Thr Pro Asp Glu Trp Trp Arg Val Thr Gln Ser Tyr Ala Arg	
2175 2180 2185	
tct act gca gtc atg tct atg gtt gga tac ata att ggc ctt gga gac	6749
Ser Thr Ala Val Met Ser Met Val Gly Tyr Ile Ile Gly Leu Gly Asp	
2190 2195 2200	
aga cat ctg gat aat gtt ctt ata gat atg acg act gga gaa gtt gtt	6797
Arg His Leu Asp Asn Val Leu Ile Asp Met Thr Thr Gly Glu Val Val	
2205 2210 2215	
cac ata gat tac aat gtt tgc ttt gaa aaa ggt aaa agc ctt aga gtt	6845
His Ile Asp Tyr Asn Val Cys Phe Glu Lys Gly Lys Ser Leu Arg Val	
2220 2225 2230 2235	
cct gag aaa gta cct ttt cga atg aca caa aac att gaa aca gca ctg	6893
Pro Glu Lys Val Pro Phe Arg Met Thr Gln Asn Ile Glu Thr Ala Leu	
2240 2245 2250	
ggc gta act gga gta gaa ggt gta ttt agg ctt tca tgt gag cag gtt	6941
Gly Val Thr Gly Val Glu Gly Val Phe Arg Leu Ser Cys Glu Gln Val	
2255 2260 2265	
tta cac att atg cgg cgt ggc aga gag acc ctg ctg acg ctg ctg gag	6989
Leu His Ile Met Arg Arg Gly Arg Glu Thr Leu Leu Thr Leu Leu Glu	
2270 2275 2280	
gcc ttt gtg tac gac cct ctg gtg gac tgg aca gca gga ggc gag gct	7037
Ala Phe Val Tyr Asp Pro Leu Val Asp Trp Thr Ala Gly Gly Glu Ala	
2285 2290 2295	
ggg ttt gct ggt gct gtc tat ggt gga ggt ggc cag cag gcc gag agc	7085
Gly Phe Ala Gly Ala Val Tyr Gly Gly Gly Gly Gln Gln Ala Glu Ser	
2300 2305 2310 2315	
aag cag agc aag aga gag atg gag cga gag atc acc cgc agc ctg ttt	7133
Lys Gln Ser Lys Arg Glu Met Glu Arg Glu Ile Thr Arg Ser Leu Phe	
2320 2325 2330	
tct tct aga gta gct gag att aag gtg aac tgg ttt aag aat aga gat	7181
Ser Ser Arg Val Ala Glu Ile Lys Val Asn Trp Phe Lys Asn Arg Asp	
2335 2340 2345	
gag atg ctg gtt gtg ctt ccc aag ttg gac ggt agc tta gat gaa tac	7229
Glu Met Leu Val Val Leu Pro Lys Leu Asp Gly Ser Leu Asp Glu Tyr	
2350 2355 2360	

cta agc ttg caa gag caa ctg aca gat gtg gaa aaa ctg cag ggc aaa	7277
Leu Ser Leu Gln Glu Gln Leu Thr Asp Val Glu Lys Leu Gln Gly Lys	
2365 2370 2375	
cta ctg gag gaa ata gag ttt cta gaa gga gct gaa ggg gtg gat cat	7325
Leu Leu Glu Glu Ile Glu Phe Leu Glu Gly Ala Glu Gly Val Asp His	
2380 2385 2390 2395	
cct tct cat act ctg caa cac agg tat tct gag cac acc caa cta cag	7373
Pro Ser His Thr Leu Gln His Arg Tyr Ser Glu His Thr Gln Leu Gln	
2400 2405 2410	
act cag caa aga gct gtt cag gaa gca atc cag gtg aag ctg aat gaa	7421
Thr Gln Gln Arg Ala Val Gln Glu Ala Ile Gln Val Lys Leu Asn Glu	
2415 2420 2425	
ttt gaa caa tgg ata aca cat tat cag gct gca ttc aat aat tta gaa	7469
Phe Glu Gln Trp Ile Thr His Tyr Gln Ala Ala Phe Asn Asn Leu Glu	
2430 2435 2440	
gca aca cag ctt gca agc ttg ctt caa gag ata agc aca caa atg gac	7517
Ala Thr Gln Leu Ala Ser Leu Leu Gln Glu Ile Ser Thr Gln Met Asp	
2445 2450 2455	
ctt ggt cct cca agt tac gtg cca gca aca gcc ttt ctg cag aat gct	7565
Leu Gly Pro Pro Ser Tyr Val Pro Ala Thr Ala Phe Leu Gln Asn Ala	
2460 2465 2470 2475	
ggt cag gcc cac ttg att agc cag tgc gag cag ctg gag ggg gag gtt	7613
Gly Gln Ala His Leu Ile Ser Gln Cys Glu Gln Leu Glu Gly Glu Val	
2480 2485 2490	
ggt gct ctc ctg cag cag agg cgc tcc gtg ctc cgt ggc tgt ctg gag	7661
Gly Ala Leu Leu Gln Gln Arg Arg Ser Val Leu Arg Gly Cys Leu Glu	
2495 2500 2505	
caa ctg cat cac tat gca acc gtg gcc ctg cag tat ccg aag gcc ata	7709
Gln Leu His His Tyr Ala Thr Val Ala Leu Gln Tyr Pro Lys Ala Ile	
2510 2515 2520	
ttt cag aaa cat cga att gaa cag tgg aag acc tgg atg gaa gag ctc	7757
Phe Gln Lys His Arg Ile Glu Gln Trp Lys Thr Trp Met Glu Glu Leu	
2525 2530 2535	
atc tgt aac acc aca gta gag cgt tgt caa gag ctc tat agg aaa tat	7805
Ile Cys Asn Thr Thr Val Glu Arg Cys Gln Glu Leu Tyr Arg Lys Tyr	
2540 2545 2550 2555	
gaa atg caa tat gct ccc cag cca ccc cca aca gtg tgt cag ttc atc	7853
Glu Met Gln Tyr Ala Pro Gln Pro Pro Pro Thr Val Cys Gln Phe Ile	
2560 2565 2570	
act gcc act gaa atg acc ctg cag cga tac gca gca gac atc aac agc	7901
Thr Ala Thr Glu Met Thr Leu Gln Arg Tyr Ala Ala Asp Ile Asn Ser	
2575 2580 2585	

aga ctt att aga caa gtg gaa cgc ttg aaa cag gaa gct gtc act gtg	7949
Arg Leu Ile Arg Gln Val Glu Arg Leu Lys Gln Glu Ala Val Thr Val	
2590 2595 2600	
cca gtt tgt gaa gat cag ttg aaa gaa att gaa cgt tgc att aaa gtt	7997
Pro Val Cys Glu Asp Gln Leu Lys Glu Ile Glu Arg Cys Ile Lys Val	
2605 2610 2615	
ttc ctt cat gag aat gga gaa gaa gga tct ttg agt cta gca agt gtt	8045
Phe Leu His Glu Asn Gly Glu Glu Gly Ser Leu Ser Leu Ala Ser Val	
2620 2625 2630 2635	
att att tct gcc ctt tgt acc ctt aca agg cgt aac ctg atg atg gaa	8093
Ile Ile Ser Ala Leu Cys Thr Leu Thr Arg Arg Asn Leu Met Met Glu	
2640 2645 2650	
ggg gca gcg tca agt gct gga gaa cag ctg gtt gat ctg act tct cgg	8141
Gly Ala Ala Ser Ser Ala Gly Glu Gln Leu Val Asp Leu Thr Ser Arg	
2655 2660 2665	
gat gga gcc tgg ttc ttg gag gaa ctc tgc agt atg agc gga aac gtc	8189
Asp Gly Ala Trp Phe Leu Glu Glu Leu Cys Ser Met Ser Gly Asn Val	
2670 2675 2680	
acc tgc ttg gtt cag tta ctg aag cag tgc cac ctg gtg cca cag gac	8237
Thr Cys Leu Val Gln Leu Leu Lys Gln Cys His Leu Val Pro Gln Asp	
2685 2690 2695	
tta gat atc ccg aac ccc atg gaa gcg tct gag aca gtt cac tta gcc	8285
Leu Asp Ile Pro Asn Pro Met Glu Ala Ser Glu Thr Val His Leu Ala	
2700 2705 2710 2715	
aat gga gtg tat acc tca ctt cag gaa ttg aat tcg aat ttc cgg caa	8333
Asn Gly Val Tyr Thr Ser Leu Gln Glu Leu Asn Ser Asn Phe Arg Gln	
2720 2725 2730	
atc ata ttt cca gaa gca ctt cga tgt tta atg aaa ggg gaa tac acg	8381
Ile Ile Phe Pro Glu Ala Leu Arg Cys Leu Met Lys Gly Glu Tyr Thr	
2735 2740 2745	
tta gaa agt atg ctg cat gaa ctg gac ggt ctt att gag cag acc acc	8429
Leu Glu Ser Met Leu His Glu Leu Asp Gly Leu Ile Glu Gln Thr Thr	
2750 2755 2760	
gat ggc gtt ccc ctg cag act cta gtg gaa tct ctt cag gcc tac tta	8477
Asp Gly Val Pro Leu Gln Thr Leu Val Glu Ser Leu Gln Ala Tyr Leu	
2765 2770 2775	
aga aac gca gct atg gga ctg gaa gaa gaa aca cat gct cat tac atc	8525
Arg Asn Ala Ala Met Gly Leu Glu Glu Glu Thr His Ala His Tyr Ile	
2780 2785 2790 2795	
gat gtt gcc aga cta cta cat gct cag tac ggt gaa tta atc caa ccg	8573
Asp Val Ala Arg Leu Leu His Ala Gln Tyr Gly Glu Leu Ile Gln Pro	

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cac aaa cag ttg acc cag gat atg tct act cag agg gca att cag aca	9917
His Lys Gln Leu Thr Gln Asp Met Ser Thr Gln Arg Ala Ile Gln Thr	
3245 3250 3255	
 gag aaa gag cag cag ata gaa acg gtc tgt gaa aca att cag aat ctg	9965
Glu Lys Glu Gln Gln Ile Glu Thr Val Cys Glu Thr Ile Gln Asn Leu	
3260 3265 3270 3275	
 gtt gat aat ata aag act gtg ctc act ggt cat aac cga cag ctt gga	10013
Val Asp Asn Ile Lys Thr Val Leu Thr Gly His Asn Arg Gln Leu Gly	
3280 3285 3290	
 gat gtc aaa cat ctc ttg aaa gct atg gct aag gat gaa gaa gct gct	10061
Asp Val Lys His Leu Leu Lys Ala Met Ala Lys Asp Glu Glu Ala Ala	
3295 3300 3305	
 ctg gca gat ggt gaa gat gtt ccc tat gag aac agt gtt agg cag ttt	10109
Leu Ala Asp Gly Glu Asp Val Pro Tyr Glu Asn Ser Val Arg Gln Phe	
3310 3315 3320	
 ttg ggt gaa tat aaa tca tgg caa gac aac att caa aca gtt cta ttt	10157
Leu Gly Glu Tyr Lys Ser Trp Gln Asp Asn Ile Gln Thr Val Leu Phe	
3325 3330 3335	
 aca tta gtc cag gct atg ggt cag gtt cga agt caa gaa cac gtt gaa	10205
Thr Leu Val Gln Ala Met Gly Gln Val Arg Ser Gln Glu His Val Glu	
3340 3345 3350 3355	
 atg ctc cag gaa atc act ccc acc ttg aaa gaa ctg aaa aca caa agt	10253
Met Leu Gln Glu Ile Thr Pro Thr Leu Lys Glu Leu Lys Thr Gln Ser	
3360 3365 3370	
 cag agt atc tat aat aat tta gtg agt ttt gca tca ccc tta gtc acc	10301
Gln Ser Ile Tyr Asn Asn Leu Val Ser Phe Ala Ser Pro Leu Val Thr	
3375 3380 3385	
 gat gca aca aat gaa tgt tcg agt cca acg tca tct gct act tat cag	10349
Asp Ala Thr Asn Glu Cys Ser Ser Pro Thr Ser Ser Ala Thr Tyr Gln	
3390 3395 3400	
 cca tcc ttc gct gca gca gtc cgg agt aac act ggc cag aag act cag	10397
Pro Ser Phe Ala Ala Ala Val Arg Ser Asn Thr Gly Gln Lys Thr Gln	
3405 3410 3415	
 cct gat gtc atg tca cag aat gct aga aag ctg atc cag aaa aat ctt	10445
Pro Asp Val Met Ser Gln Asn Ala Arg Lys Leu Ile Gln Lys Asn Leu	
3420 3425 3430 3435	
 gct aca tca gct gat act cca cca agc acc gtt cca gga act ggc aag	10493
Ala Thr Ser Ala Asp Thr Pro Pro Ser Thr Val Pro Gly Thr Gly Lys	
3440 3445 3450	
 agt gtt gct tgt agt cct aaa aag gca gtc aga gac cct aaa act ggg	10541
Ser Val Ala Cys Ser Pro Lys Lys Ala Val Arg Asp Pro Lys Thr Gly	
3455 3460 3465	

aaa gcg gtg caa gag aga aac tcc tat gca gtg agt gtg tgg aag aga 10589
 Lys Ala Val Gln Glu Arg Asn Ser Tyr Ala Val Ser Val Trp Lys Arg
 3470 3475 3480

gtg aaa gcc aag tta gag ggc cga gat gtt gat ccg aat agg agg atg 10637
 Val Lys Ala Lys Leu Glu Gly Arg Asp Val Asp Pro Asn Arg Arg Met
 3485 3490 3495

tca gtt gct gaa cag gtt gac tat gtc att aag gaa gca act aat cta 10685
 Ser Val Ala Glu Gln Val Asp Tyr Val Ile Lys Glu Ala Thr Asn Leu
 3500 3505 3510 3515

gat aac ttg gct cag ctg tat gaa ggt tgg aca gcc tgg gtg tga 10730
 Asp Asn Leu Ala Gln Leu Tyr Glu Gly Trp Thr Ala Trp Val *
 3520 3525

atggcaagac agtagatgag tctgggtaag cgaggtcaga catccaccag aatcaactca 10790
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<212> PRT

<213> Homo sapiens

<400> 8

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Met Ser Arg Arg Ala Pro Gly Ser Arg

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Pro Arg Thr Asp Ser Ala Ser Ala Asp Pro Gly Asn Leu Lys Tyr Ser
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140 145 150

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Glu Ser Val Asp Glu Asp Val Pro Pro Pro Ser Val Ser Leu Pro Lys	
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Trp Ala Leu Glu Ala Ala Val Leu Met Arg Lys Ser Glu Thr Tyr Ala				
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Ser Leu His Ala Leu Ser Ser Ser Leu Pro Asp Asp Leu Leu Gln Arg				
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 Pro Glu Ala Ile Gln Gly Ile Ala Val Trp Ser Ser Ser Ile Val Gly
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Val Arg Pro Trp Met Gln Ala Leu Arg Tyr Thr Met Tyr Gln Asn Gln	
1390 1395 1400	
ttg ttg gag aaa att aaa gaa caa aca gtc cca att aga agc cat ctc	4578
Leu Leu Glu Lys Ile Lys Glu Gln Thr Val Pro Ile Arg Ser His Leu	
1405 1410 1415	
atg gaa tta ggt cta aca gca gca aaa ttt gct aga aaa cga ggg aat	4626
Met Glu Leu Gly Leu Thr Ala Ala Lys Phe Ala Arg Lys Arg Gly Asn	
1420 1425 1430	
gtg tcc ctt gca aca aga ctg ctg gca cag tgc agt gaa gtt cag ctg	4674
Val Ser Leu Ala Thr Arg Leu Leu Ala Gln Cys Ser Glu Val Gln Leu	
1435 1440 1445	
gga aag acc acc act gca cag gat tta gtc caa cat ttt aaa aaa cta	4722
Gly Lys Thr Thr Thr Ala Gln Asp Leu Val Gln His Phe Lys Lys Leu	

1450	1455	1460	1465	
tca acc caa ggt caa gtg gat gaa aaa tgg ggg ccc gaa ctt gat att				4770
Ser Thr Gln Gly Gln Val Asp Glu Lys Trp Gly Pro Glu Leu Asp Ile				
	1470	1475	1480	
gaa aaa acc aaa ttg ctt tat aca gca ggc cag tca aca cat gca atg				4818
Glu Lys Thr Lys Leu Leu Tyr Thr Ala Gly Gln Ser Thr His Ala Met				
	1485	1490	1495	
gaa atg ttg agt tct tgt gcc ata tct ttc tgc aag tct gtg aaa gct				4866
Glu Met Leu Ser Ser Cys Ala Ile Ser Phe Cys Lys Ser Val Lys Ala				
	1500	1505	1510	
gaa tat gca gtt gct aaa tca att ctg aca ctg gct aaa tgg atc cag				4914
Glu Tyr Ala Val Ala Lys Ser Ile Leu Thr Leu Ala Lys Trp Ile Gln				
	1515	1520	1525	
gca gaa tgg aaa gag att tca gga cag ctg aaa cag gtt tac aga gct				4962
Ala Glu Trp Lys Glu Ile Ser Gly Gln Leu Lys Gln Val Tyr Arg Ala				
	1530	1535	1540	1545
cag cac caa cag aac ttc aca ggt ctt tct act ttg tct aaa aac ata				5010
Gln His Gln Gln Asn Phe Thr Gly Leu Ser Thr Leu Ser Lys Asn Ile				
	1550	1555	1560	
ctc act cta ata gaa ctg cca tct gtt aat acg atg gaa gaa gag tat				5058
Leu Thr Leu Ile Glu Leu Pro Ser Val Asn Thr Met Glu Glu Glu Tyr				
	1565	1570	1575	
cct cgg atc gag agt gaa tct aca gtg cat att gga gtt gga gaa cct				5106
Pro Arg Ile Glu Ser Glu Ser Thr Val His Ile Gly Val Gly Glu Pro				
	1580	1585	1590	
gac ttc att ttg gga cag ttg tat cac ctg tct tca gta cag gca cct				5154
Asp Phe Ile Leu Gly Gln Leu Tyr His Leu Ser Ser Val Gln Ala Pro				
	1595	1600	1605	
gaa gta gcc aaa tct tgg gca gcg ttg gcc agc tgg gct tat agg tgg				5202
Glu Val Ala Lys Ser Trp Ala Ala Leu Ala Ser Trp Ala Tyr Arg Trp				
	1610	1615	1620	1625
ggc aga aag gtg gtt gac aat gcc agt cag gga gaa ggt gtt cgt ctg				5250
Gly Arg Lys Val Val Asp Asn Ala Ser Gln Gly Glu Gly Val Arg Leu				
	1630	1635	1640	
ctg cct aga gaa aaa tct gaa gtt cag aat cta ctt cca gac act ata				5298
Leu Pro Arg Glu Lys Ser Glu Val Gln Asn Leu Leu Pro Asp Thr Ile				
	1645	1650	1655	
act gag gaa gag aaa gag aga ata tat ggt att ctt gga cag gct gtg				5346
Thr Glu Glu Glu Lys Glu Arg Ile Tyr Gly Ile Leu Gly Gln Ala Val				
	1660	1665	1670	
tgt cgg ccg gcg ggg att cag gat gaa gat ata aca ctt cag ata act				5394

Cys Arg Pro Ala Gly Ile Gln Asp Glu Asp Ile Thr Leu Gln Ile Thr	
1675	1680 1685
gag agt gaa gac aac gaa gaa gat gac atg gtt gat gtt atc tgg cgt 5442	
Glu Ser Glu Asp Asn Glu Glu Asp Asp Met Val Asp Val Ile Trp Arg	
1690	1695 1700 1705
cag ttg ata tca agc tgc cca tgg ctt tca gaa ctt gat gaa agt gca 5490	
Gln Leu Ile Ser Ser Cys Pro Trp Leu Ser Glu Leu Asp Glu Ser Ala	
	1710 1715 1720
act gaa gga gtt att aaa gtg tgg agg aaa gtt gta gat aga ata ttc 5538	
Thr Glu Gly Val Ile Lys Val Trp Arg Lys Val Val Asp Arg Ile Phe	
	1725 1730 1735
agc ctg tac aaa ctc tct tgc agt gca tac ttt act ttc ctt aaa ctc 5586	
Ser Leu Tyr Lys Leu Ser Cys Ser Ala Tyr Phe Thr Phe Leu Lys Leu	
	1740 1745 1750
aac gct ggt caa att cct tta gat gag gat gac cct agg ctg cat tta 5634	
Asn Ala Gly Gln Ile Pro Leu Asp Glu Asp Asp Pro Arg Leu His Leu	
	1755 1760 1765
agt cac aga gtg gaa cag agc act gat gac atg att gtg atg gcc aca 5682	
Ser His Arg Val Glu Gln Ser Thr Asp Asp Met Ile Val Met Ala Thr	
1770	1775 1780 1785
ttg cgc ctg ctg cgg ttg ctc gtg aag cat gct ggt gag ctt cgg cag 5730	
Leu Arg Leu Leu Arg Leu Leu Val Lys His Ala Gly Glu Leu Arg Gln	
	1790 1795 1800
tat ctg gag cac ggc ttg gag aca aca ccc act gca cca tgg agg gga 5778	
Tyr Leu Glu His Gly Leu Glu Thr Thr Pro Thr Ala Pro Trp Arg Gly	
	1805 1810 1815
att att ccg caa ctt ttc tca cgc tta aac cac cct gaa gtg tat gtg 5826	
Ile Ile Pro Gln Leu Phe Ser Arg Leu Asn His Pro Glu Val Tyr Val	
	1820 1825 1830
cgc caa agt att tgt aac ctt ctc tgc cgt gtg gct caa gat tcc cca 5874	
Arg Gln Ser Ile Cys Asn Leu Leu Cys Arg Val Ala Gln Asp Ser Pro	
	1835 1840 1845
cat ctc ata ttg tat cct gca ata gtg ggt acc ata tcg ctt agt agt 5922	
His Leu Ile Leu Tyr Pro Ala Ile Val Gly Thr Ile Ser Leu Ser Ser	
1850	1855 1860 1865
gaa tcc cag gct tca gga aat aaa ttt tcc act gca att cca act tta 5970	
Glu Ser Gln Ala Ser Gly Asn Lys Phe Ser Thr Ala Ile Pro Thr Leu	
	1870 1875 1880
ctt ggc aat att caa gga gaa gaa ttg ctg gtt tct gaa tgt gag gga 6018	
Leu Gly Asn Ile Gln Gly Glu Glu Leu Leu Val Ser Glu Cys Glu Gly	
	1885 1890 1895

gga agt cct cct gca tct cag gat agc aat aag gat gaa cct aaa agt	6066
Gly Ser Pro Pro Ala Ser Gln Asp Ser Asn Lys Asp Glu Pro Lys Ser	
1900 1905 1910	
gga tta aat gaa gac caa gcc atg atg cag gat tgt tac agc aaa att	6114
Gly Leu Asn Glu Asp Gln Ala Met Met Gln Asp Cys Tyr Ser Lys Ile	
1915 1920 1925	
gta gat aag ctg tcc tct gca aac ccc acc atg gta tta cag gtt cag	6162
Val Asp Lys Leu Ser Ser Ala Asn Pro Thr Met Val Leu Gln Val Gln	
1930 1935 1940 1945	
atg ctc gtg gct gaa ctg cgc agg gtc act gtg ctc tgg gat gag ctc	6210
Met Leu Val Ala Glu Leu Arg Arg Val Thr Val Leu Trp Asp Glu Leu	
1950 1955 1960	
tgg ctg gga gtt ttg ctg caa caa cac atg tat gtc ctg aga cga att	6258
Trp Leu Gly Val Leu Leu Gln Gln His Met Tyr Val Leu Arg Arg Ile	
1965 1970 1975	
cag cag ctt gaa gat gag gtg aag aga gtc cag aac aac aac acc tta	6306
Gln Gln Leu Glu Asp Glu Val Lys Arg Val Gln Asn Asn Asn Thr Leu	
1980 1985 1990	
cgc aaa gaa gag aaa att gca atc atg agg gag agg cac aca gct ttg	6354
Arg Lys Glu Glu Lys Ile Ala Ile Met Arg Glu Arg His Thr Ala Leu	
1995 2000 2005	
atg aag ccc atc gta ttt gct ttg gag cat gtg agg agt atc aca gcg	6402
Met Lys Pro Ile Val Phe Ala Leu Glu His Val Arg Ser Ile Thr Ala	
2010 2015 2020 2025	
gct cct gca gaa aca cct cat gaa aaa tgg ttt cag gat aac tat ggt	6450
Ala Pro Ala Glu Thr Pro His Glu Lys Trp Phe Gln Asp Asn Tyr Gly	
2030 2035 2040	
gat gcc att gaa aat gcc cta gaa aaa ctg aag act cca ttg aac cct	6498
Asp Ala Ile Glu Asn Ala Leu Glu Lys Leu Lys Thr Pro Leu Asn Pro	
2045 2050 2055	
gca aag cct ggg agc agc tgg att cca ttt aaa gag ata atg cta agt	6546
Ala Lys Pro Gly Ser Ser Trp Ile Pro Phe Lys Glu Ile Met Leu Ser	
2060 2065 2070	
ttg caa cag aga gca cag aaa cgt gca agt tac atc ttg cgt ctt gaa	6594
Leu Gln Gln Arg Ala Gln Lys Arg Ala Ser Tyr Ile Leu Arg Leu Glu	
2075 2080 2085	
gaa atc agt cca tgg ttg gct gcc atg act aac act gaa att gct ctt	6642
Glu Ile Ser Pro Trp Leu Ala Ala Met Thr Asn Thr Glu Ile Ala Leu	
2090 2095 2100 2105	
cct ggg gaa gtc tca gcc aga gac act gtc aca atc cat agt gtg ggc	6690
Pro Gly Glu Val Ser Ala Arg Asp Thr Val Thr Ile His Ser Val Gly	
2110 2115 2120	

gga acc atc aca atc tta ccg act aaa acc aag cca aag aaa ctt ctc	6738
Gly Thr Ile Thr Ile Leu Pro Thr Lys Thr Lys Pro Lys Lys Leu Leu	
2125 2130 2135	
ttt ctt gga tca gat ggg aag agc tat cct tat ctt ttc aaa gga ctg	6786
Phe Leu Gly Ser Asp Gly Lys Ser Tyr Pro Tyr Leu Phe Lys Gly Leu	
2140 2145 2150	
gag gat tta cat ctg gat gag aga ata atg cag ttc cta tct att gtg	6834
Glu Asp Leu His Leu Asp Glu Arg Ile Met Gln Phe Leu Ser Ile Val	
2155 2160 2165	
aat acc atg ttt gct aca att aat cgc caa gaa aca ccc cgg ttc cat	6882
Asn Thr Met Phe Ala Thr Ile Asn Arg Gln Glu Thr Pro Arg Phe His	
2170 2175 2180 2185	
gct cga cac tat tct gta aca cca cta gga aca aga tca gga cta atc	6930
Ala Arg His Tyr Ser Val Thr Pro Leu Gly Thr Arg Ser Gly Leu Ile	
2190 2195 2200	
cag tgg gta gat gga gcc aca ccc tta ttt ggt ctt tac aaa cga tgg	6978
Gln Trp Val Asp Gly Ala Thr Pro Leu Phe Gly Leu Tyr Lys Arg Trp	
2205 2210 2215	
caa caa cgg gaa gct gcc tta caa gca caa aag gcc caa gat tcc tac	7026
Gln Gln Arg Glu Ala Ala Leu Gln Ala Gln Lys Ala Gln Asp Ser Tyr	
2220 2225 2230	
caa act cct cag aat cct gga att gta ccc cgt cct agt gaa ctt tat	7074
Gln Thr Pro Gln Asn Pro Gly Ile Val Pro Arg Pro Ser Glu Leu Tyr	
2235 2240 2245	
tac agt aaa att ggc cct gct ttg aaa aca gtt ggg ctt agc ctg gat	7122
Tyr Ser Lys Ile Gly Pro Ala Leu Lys Thr Val Gly Leu Ser Leu Asp	
2250 2255 2260 2265	
gtg tcc cgt cgg gat tgg cct ctt cat gta atg aag gca gta ttg gaa	7170
Val Ser Arg Arg Asp Trp Pro Leu His Val Met Lys Ala Val Leu Glu	
2270 2275 2280	
gag tta atg gag gcc aca ccc ccg aat ctc ctt gcc aaa gag ctc tgg	7218
Glu Leu Met Glu Ala Thr Pro Pro Asn Leu Leu Ala Lys Glu Leu Trp	
2285 2290 2295	
tca tct tgc aca aca cct gat gaa tgg tgg aga gtt acg cag tct tat	7266
Ser Ser Cys Thr Thr Pro Asp Glu Trp Trp Arg Val Thr Gln Ser Tyr	
2300 2305 2310	
gca aga tct act gca gtc atg tct atg gtt gga tac ata att ggc ctt	7314
Ala Arg Ser Thr Ala Val Met Ser Met Val Gly Tyr Ile Ile Gly Leu	
2315 2320 2325	
gga gac aga cat ctg gat aat gtt ctt ata gat atg acg act gga gaa	7362
Gly Asp Arg His Leu Asp Asn Val Leu Ile Asp Met Thr Thr Gly Glu	

2330	2335	2340	2345	
gtt gtt cac ata gat tac aat gtt tgc ttt gaa aaa ggt aaa agc ctt				7410
Val Val His Ile Asp Tyr Asn Val Cys Phe Glu Lys Gly Lys Ser Leu				
	2350	2355	2360	
aga gtt cct gag aaa gta cct ttt cga atg aca caa aac att gaa aca				7458
Arg Val Pro Glu Lys Val Pro Phe Arg Met Thr Gln Asn Ile Glu Thr				
	2365	2370	2375	
gca ctg ggt gta act gga gta gaa ggt gta ttt agg ctt tca tgt gag				7506
Ala Leu Gly Val Thr Gly Val Glu Gly Val Phe Arg Leu Ser Cys Glu				
	2380	2385	2390	
cag gtt tta cac att atg cgg cgt ggc aga gag acc ctg ctg acg ctg				7554
Gln Val Leu His Ile Met Arg Arg Gly Arg Glu Thr Leu Leu Thr Leu				
	2395	2400	2405	
ctg gag gcc ttt gtg tac gac cct ctg gtg gac tgg aca gca gga ggc				7602
Leu Glu Ala Phe Val Tyr Asp Pro Leu Val Asp Trp Thr Ala Gly Gly				
	2410	2415	2420	2425
gag gct ggg ttt gct ggt gct gtc tat ggt gga ggt ggc cag cag gcc				7650
Glu Ala Gly Phe Ala Gly Ala Val Tyr Gly Gly Gly Gly Gln Gln Ala				
	2430	2435	2440	
gag agc aag cag agc aag aga gag atg gag cga gag atc acc cgc agc				7698
Glu Ser Lys Gln Ser Lys Arg Glu Met Glu Arg Glu Ile Thr Arg Ser				
	2445	2450	2455	
ctg ttt tct tct aga gta gct gag att aag gtg aac tgg ttt aag aat				7746
Leu Phe Ser Ser Arg Val Ala Glu Ile Lys Val Asn Trp Phe Lys Asn				
	2460	2465	2470	
aga gat gag atg ctg gtt gtg ctt ccc aag ttg gac ggt agc tta gat				7794
Arg Asp Glu Met Leu Val Val Leu Pro Lys Leu Asp Gly Ser Leu Asp				
	2475	2480	2485	
gaa tac cta agc ttg caa gag caa ctg aca gat gtg gaa aaa ctg cag				7842
Glu Tyr Leu Ser Leu Gln Glu Gln Leu Thr Asp Val Glu Lys Leu Gln				
	2490	2495	2500	2505
ggc aaa cta ctg gag gaa ata gag ttt cta gaa gga gct gaa ggg gtg				7890
Gly Lys Leu Leu Glu Glu Ile Glu Phe Leu Glu Gly Ala Glu Gly Val				
	2510	2515	2520	
gat cat cct tct cat act ctg caa cac agg tat tct gag cac acc caa				7938
Asp His Pro Ser His Thr Leu Gln His Arg Tyr Ser Glu His Thr Gln				
	2525	2530	2535	
cta cag act cag caa aga gct gtt cag gaa gca atc cag gtg aag ctg				7986
Leu Gln Thr Gln Gln Arg Ala Val Gln Glu Ala Ile Gln Val Lys Leu				
	2540	2545	2550	
aat gaa ttt gaa caa tgg ata aca cat tat cag gct gca ttc aat aat				8034

Asn Glu Phe Glu Gln Trp	Ile Thr His Tyr Gln Ala Ala Phe Asn Asn	
2555	2560	2565
tta gaa gca aca cag ctt gca agc ttg ctt caa gag ata agc aca caa		8082
Leu Glu Ala Thr Gln Leu Ala Ser Leu Leu Gln Glu Ile Ser Thr Gln		
2570	2575	2580 2585
atg gac ctt ggt cct cca agt tac gtg cca gca aca gcc ttt ctg cag		8130
Met Asp Leu Gly Pro Pro Ser Tyr Val Pro Ala Thr Ala Phe Leu Gln		
2590	2595	2600
aat gct ggt cag gcc cac ttg att agc cag tgc gag cag ctg gag ggg		8178
Asn Ala Gly Gln Ala His Leu Ile Ser Gln Cys Glu Gln Leu Glu Gly		
2605	2610	2615
gag gtt ggt gct ctc ctg cag cag agg cgc tcc gtg ctc cgt ggc tgt		8226
Glu Val Gly Ala Leu Leu Gln Gln Arg Arg Ser Val Leu Arg Gly Cys		
2620	2625	2630
ctg gag caa ctg cat cac tat gca acc gtg gcc ctg cag tat ccg aag		8274
Leu Glu Gln Leu His His Tyr Ala Thr Val Ala Leu Gln Tyr Pro Lys		
2635	2640	2645
gcc ata ttt cag aaa cat cga att gaa cag tgg aag acc tgg atg gaa		8322
Ala Ile Phe Gln Lys His Arg Ile Glu Gln Trp Lys Thr Trp Met Glu		
2650	2655	2660 2665
gag ctc atc tgt aac acc aca gta gag cgt tgt caa gag ctc tat agg		8370
Glu Leu Ile Cys Asn Thr Thr Val Glu Arg Cys Gln Glu Leu Tyr Arg		
2670	2675	2680
aaa tat gaa atg caa tat gct ccc cag cca ccc cca aca gtg tgt cag		8418
Lys Tyr Glu Met Gln Tyr Ala Pro Gln Pro Pro Pro Thr Val Cys Gln		
2685	2690	2695
ttc atc act gcc act gaa atg acc ctg cag cga tac gca gca gac atc		8466
Phe Ile Thr Ala Thr Glu Met Thr Leu Gln Arg Tyr Ala Ala Asp Ile		
2700	2705	2710
aac agc aga ctt att aga caa gtg gaa cgc ttg aaa cag gaa gct gtc		8514
Asn Ser Arg Leu Ile Arg Gln Val Glu Arg Leu Lys Gln Glu Ala Val		
2715	2720	2725
act gtg cca gtt tgt gaa gat cag ttg aaa gaa att gaa cgt tgc att		8562
Thr Val Pro Val Cys Glu Asp Gln Leu Lys Glu Ile Glu Arg Cys Ile		
2730	2735	2740 2745
aaa gtt ttc ctt cat gag aat gga gaa gaa gga tct ttg agt cta gca		8610
Lys Val Phe Leu His Glu Asn Gly Glu Glu Gly Ser Leu Ser Leu Ala		
2750	2755	2760
agt gtt att att tct gcc ctt tgt acc ctt aca agg cgt aac ctg atg		8658
Ser Val Ile Ile Ser Ala Leu Cys Thr Leu Thr Arg Arg Asn Leu Met		
2765	2770	2775

atg gaa ggt gca gcg tca agt gct gga gaa cag ctg gtt gat ctg act	8706
Met Glu Gly Ala Ala Ser Ser Ala Gly Glu Gln Leu Val Asp Leu Thr	
2780 2785 2790	
tct cgg gat gga gcc tgg ttc ttg gag gaa ctc tgc agt atg agc gga	8754
Ser Arg Asp Gly Ala Trp Phe Leu Glu Glu Leu Cys Ser Met Ser Gly	
2795 2800 2805	
aac gtc acc tgc ttg gtt cag tta ctg aag cag tgc cac ctg gtg cca	8802
Asn Val Thr Cys Leu Val Gln Leu Leu Lys Gln Cys His Leu Val Pro	
2810 2815 2820 2825	
cag gac tta gat atc ccg aac ccc atg gaa gcg tct gag aca gtt cac	8850
Gln Asp Leu Asp Ile Pro Asn Pro Met Glu Ala Ser Glu Thr Val His	
2830 2835 2840	
tta gcc aat gga gtg tat acc tca ctt cag gaa ttg aat tcg aat ttc	8898
Leu Ala Asn Gly Val Tyr Thr Ser Leu Gln Glu Leu Asn Ser Asn Phe	
2845 2850 2855	
cgg caa atc ata ttt cca gaa gca ctt cga tgt tta atg aaa ggg gaa	8946
Arg Gln Ile Ile Phe Pro Glu Ala Leu Arg Cys Leu Met Lys Gly Glu	
2860 2865 2870	
tac acg tta gaa agt atg ctg cat gaa ctg gac ggt ctt att gag cag	8994
Tyr Thr Leu Glu Ser Met Leu His Glu Leu Asp Gly Leu Ile Glu Gln	
2875 2880 2885	
acc acc gat ggc gtt ccc ctg cag act cta gtg gaa tct ctt cag gcc	9042
Thr Thr Asp Gly Val Pro Leu Gln Thr Leu Val Glu Ser Leu Gln Ala	
2890 2895 2900 2905	
tac tta aga aac gca gct atg gga ctg gaa gaa gaa aca cat gct cat	9090
Tyr Leu Arg Asn Ala Ala Met Gly Leu Glu Glu Glu Thr His Ala His	
2910 2915 2920	
tac atc gat gtt gcc aga cta cta cat gct cag tac ggt gaa tta atc	9138
Tyr Ile Asp Val Ala Arg Leu Leu His Ala Gln Tyr Gly Glu Leu Ile	
2925 2930 2935	
caa ccg aga aat ggt tca gtt gat gaa aca ccc aaa atg tca gct ggc	9186
Gln Pro Arg Asn Gly Ser Val Asp Glu Thr Pro Lys Met Ser Ala Gly	
2940 2945 2950	
cag atg ctt ttg gta gca ttc gat ggc atg ttt gct caa gtt gaa act	9234
Gln Met Leu Leu Val Ala Phe Asp Gly Met Phe Ala Gln Val Glu Thr	
2955 2960 2965	
gct ttc agc tta tta gtt gaa aag ttg aac aag atg gaa att ccc ata	9282
Ala Phe Ser Leu Leu Val Glu Lys Leu Asn Lys Met Glu Ile Pro Ile	
2970 2975 2980 2985	
gct tgg cga aag att gac atc ata agg gaa gcc agg agt act caa gtt	9330
Ala Trp Arg Lys Ile Asp Ile Ile Arg Glu Ala Arg Ser Thr Gln Val	
2990 2995 3000	

aat ttt ttt gat gat gat aat cac cgg cag gtg cta gaa gag att ttc	9378
Asn Phe Phe Asp Asp Asp Asn His Arg Gln Val Leu Glu Glu Ile Phe	
3005 3010 3015	
ttt cta aaa aga cta cag act att aag gag ttc ttc agg ctc tgt ggt	9426
Phe Leu Lys Arg Leu Gln Thr Ile Lys Glu Phe Phe Arg Leu Cys Gly	
3020 3025 3030	
acc ttt tct aaa aca ttg tca gga tca agt tca ctt gaa gat cag aat	9474
Thr Phe Ser Lys Thr Leu Ser Gly Ser Ser Ser Leu Glu Asp Gln Asn	
3035 3040 3045	
act gtg aat ggg cct gta cag att gtc aat gtg aaa acc ctt ttt aga	9522
Thr Val Asn Gly Pro Val Gln Ile Val Asn Val Lys Thr Leu Phe Arg	
3050 3055 3060 3065	
aac tct tgt ttc agt gaa gac caa atg gcc aaa cct atc aag gca ttc	9570
Asn Ser Cys Phe Ser Glu Asp Gln Met Ala Lys Pro Ile Lys Ala Phe	
3070 3075 3080	
aca gct gac ttt gtg agg cag ctc ttg ata ggg cta ccc aac caa gcc	9618
Thr Ala Asp Phe Val Arg Gln Leu Leu Ile Gly Leu Pro Asn Gln Ala	
3085 3090 3095	
ctc gga ctc aca ctg tgc agt ttt atc agt gct ctg ggt gta gac atc	9666
Leu Gly Leu Thr Leu Cys Ser Phe Ile Ser Ala Leu Gly Val Asp Ile	
3100 3105 3110	
att gct caa gta gag gca aag gac ttt ggt gcc gaa agc aaa gtt tct	9714
Ile Ala Gln Val Glu Ala Lys Asp Phe Gly Ala Glu Ser Lys Val Ser	
3115 3120 3125	
gtt gat gat ctc tgt aag aaa gcg gtg gaa cat aac atc cag ata ggg	9762
Val Asp Asp Leu Cys Lys Lys Ala Val Glu His Asn Ile Gln Ile Gly	
3130 3135 3140 3145	
aag ttc tct cag ctg gtt atg aac agg gca act gtg tta gca agt tct	9810
Lys Phe Ser Gln Leu Val Met Asn Arg Ala Thr Val Leu Ala Ser Ser	
3150 3155 3160	
tac gac act gcc tgg aag aag cat gac ttg gtg cga agg cta gaa acc	9858
Tyr Asp Thr Ala Trp Lys Lys His Asp Leu Val Arg Arg Leu Glu Thr	
3165 3170 3175	
agt att tct tct tgt aag aca agc ctg cag cgg gtt cag ctg cat att	9906
Ser Ile Ser Ser Cys Lys Thr Ser Leu Gln Arg Val Gln Leu His Ile	
3180 3185 3190	
gcc atg ttt cag tgg caa cat gaa gat cta ctt atc aat aga cca caa	9954
Ala Met Phe Gln Trp Gln His Glu Asp Leu Leu Ile Asn Arg Pro Gln	
3195 3200 3205	
gcc atg tca gtc aca cct ccc cca cgg tct gct atc cta acc agc atg	10002
Ala Met Ser Val Thr Pro Pro Pro Arg Ser Ala Ile Leu Thr Ser Met	

3210	3215	3220	3225	
aaa aag aag ctg cat acc ctg agc cag att gaa act tct att gcg aca				10050
Lys Lys Lys Leu His Thr Leu Ser Gln Ile Glu Thr Ser Ile Ala Thr				
	3230	3235	3240	
gtt cag gag aag cta gct gca ctt gaa tca agt att gaa cag cga ctc				10098
Val Gln Glu Lys Leu Ala Ala Leu Glu Ser Ser Ile Glu Gln Arg Leu				
	3245	3250	3255	
aag tgg gca ggt ggt gcc aac cct gca ttg gcc cct gta cta caa gat				10146
Lys Trp Ala Gly Gly Ala Asn Pro Ala Leu Ala Pro Val Leu Gln Asp				
	3260	3265	3270	
ttt gaa gca acg ata gct gaa aga aga aat ctt gtc ctt aaa gag agc				10194
Phe Glu Ala Thr Ile Ala Glu Arg Arg Asn Leu Val Leu Lys Glu Ser				
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caa aga gca agt cag gtc aca ttt ctc tgc agc aat atc att cat ttt				10242
Gln Arg Ala Ser Gln Val Thr Phe Leu Cys Ser Asn Ile Ile His Phe				
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gaa agt tta cga aca aga act gca gaa gcc tta aac ctg gat gcg gcg				10290
Glu Ser Leu Arg Thr Arg Thr Ala Glu Ala Leu Asn Leu Asp Ala Ala				
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Leu Phe Glu Leu Ile Lys Arg Cys Gln Gln Met Cys Ser Phe Ala Ser				
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Gln Phe Asn Ser Ser Val Ser Glu Leu Glu Leu Arg Leu Leu Gln Arg				
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Val Asp Thr Gly Leu Glu His Pro Ile Gly Ser Ser Glu Trp Leu Leu				
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tca gca cac aaa cag ttg acc cag gat atg tct act cag agg gca att				10482
Ser Ala His Lys Gln Leu Thr Gln Asp Met Ser Thr Gln Arg Ala Ile				
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cag aca gag aaa gag cag cag ata gaa acg gtc tgt gaa aca att cag				10530
Gln Thr Glu Lys Glu Gln Gln Ile Glu Thr Val Cys Glu Thr Ile Gln				
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aat ctg gtt gat aat ata aag act gtg ctc act ggt cat aac cga cag				10578
Asn Leu Val Asp Asn Ile Lys Thr Val Leu Thr Gly His Asn Arg Gln				
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ctt gga gat gtc aaa cat ctc ttg aaa gct atg gct aag gat gaa gaa				10626
Leu Gly Asp Val Lys His Leu Leu Lys Ala Met Ala Lys Asp Glu Glu				
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<212> PRT

<213> Homo sapiens

<400> 10

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Tyr Ser Arg Ser Trp Asn Asp Trp Gln Pro Arg Thr Asp Ser Ala Ser
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Ala Asp Pro Gly Asn Leu Lys Tyr Ser Ser Ser Arg Asp Arg Gly Gly
          35          40          45
Ser Ser Ser Tyr Gly Leu Gln Pro Ser Asn Ser Ala Val Val Ser Arg
          50          55          60
Gln Arg His Asp Asp Thr Arg Val His Ala Asp Ile Gln Asn Asp Glu
65          70          75          80
Lys Gly Gly Tyr Ser Val Asn Gly Gly Ser Gly Glu Asn Thr Tyr Gly
          85          90          95
Arg Lys Ser Leu Gly Gln Glu Leu Arg Val Asn Asn Val Thr Ser Pro
          100          105          110
Glu Phe Thr Ser Val Gln His Gly Ser Arg Ala Leu Ala Thr Lys Asp
          115          120          125
Met Arg Lys Ser Gln Glu Arg Ser Met Ser Tyr Ser Asp Glu Ser Arg

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Leu Ser Asn Leu Leu Arg Arg Ile Thr Arg Glu Asp Asp Arg Asp Arg		
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Arg Leu Ala Thr Val Lys Gln Leu Lys Glu Phe Ile Gln Gln Pro Glu		160
	165	170
Asn Lys Leu Val Leu Val Lys Gln Leu Asp Asn Ile Leu Ala Ala Val		175
	180	185
His Asp Val Leu Asn Glu Ser Ser Lys Leu Leu Gln Glu Leu Arg Gln		190
	195	200
Glu Gly Ala Cys Cys Leu Gly Leu Leu Cys Ala Ser Leu Ser Tyr Glu		205
	210	215
Ala Glu Lys Ile Phe Lys Trp Ile Phe Ser Lys Phe Ser Ser Ser Ala		220
225	230	235
Lys Asp Glu Val Lys Leu Leu Tyr Leu Cys Ala Thr Tyr Lys Ala Leu		240
	245	250
Glu Thr Val Gly Glu Lys Lys Ala Phe Ser Ser Val Met Gln Leu Val		255
	260	265
Met Thr Ser Leu Gln Ser Ile Leu Glu Asn Val Asp Thr Pro Glu Leu		270
	275	280
Leu Cys Lys Cys Val Lys Cys Ile Leu Leu Val Ala Arg Cys Tyr Pro		285
	290	295
His Ile Phe Ser Thr Asn Phe Arg Asp Thr Val Asp Ile Leu Val Gly		300
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Trp His Ile Asp His Thr Gln Lys Pro Ser Leu Thr Gln Gln Val Ser		320
	325	330
Gly Trp Leu Gln Ser Leu Glu Pro Phe Trp Val Ala Asp Leu Ala Phe		335
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Ser Thr Thr Leu Leu Gly Gln Phe Leu Glu Asp Met Glu Ala Tyr Ala		350
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Glu Asp Leu Ser His Val Ala Ser Gly Glu Ser Val Asp Glu Asp Val		365
	370	375
Pro Pro Pro Ser Val Ser Leu Pro Lys Leu Ala Ala Leu Leu Arg Val		380
385	390	395
Phe Ser Thr Val Val Arg Ser Ile Gly Glu Arg Phe Ser Pro Ile Arg		400
	405	410
Gly Pro Pro Ile Thr Glu Ala Tyr Val Thr Asp Val Leu Tyr Arg Val		415
	420	425
Met Arg Cys Val Thr Ala Ala Asn Gln Val Phe Phe Ser Glu Ala Val		430
	435	440
Leu Thr Ala Ala Asn Glu Cys Val Gly Val Leu Leu Gly Ser Leu Asp		445
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Pro Ser Met Thr Ile His Cys Asp Met Val Ile Thr Tyr Gly Leu Asp		460
465	470	475
Gln Leu Glu Asn Cys Gln Thr Cys Gly Thr Asp Tyr Ile Ile Ser Val		480
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Leu Asn Leu Leu Thr Leu Ile Val Glu Gln Ile Asn Thr Lys Leu Pro		495
	500	505
Ser Ser Phe Val Glu Lys Leu Phe Ile Pro Ser Ser Lys Leu Leu Phe		510
	515	520
Leu Arg Tyr His Lys Glu Lys Glu Val Val Ala Val Ala His Ala Val		525
	530	535
Tyr Gln Ala Val Leu Ser Leu Lys Asn Ile Pro Val Leu Glu Thr Ala		540
545	550	555
Tyr Lys Leu Ile Leu Gly Glu Met Thr Cys Ala Leu Asn Asn Leu Leu		560
	565	570
		575

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

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Arg Ile Arg Leu Ser Ile Met Arg Val Gly Leu Leu Ala Gly Gln Pro			
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Ala Val Thr Val Arg His Gly Phe Asp Leu Leu Thr Glu Met Lys Thr			
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Thr Ser Leu Ser Gln Gly Asn Glu Leu Glu Val Thr Ile Met Met Val			
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Val Glu Ala Leu Cys Glu Leu His Cys Pro Glu Ala Ile Gln Gly Ile			
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Ala Val Trp Ser Ser Ser Ile Val Gly Lys Asn Leu Leu Trp Ile Asn			
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Ser Val Ala Gln Gln Ala Glu Gly Arg Phe Glu Lys Ala Ser Val Glu			
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Tyr Gln Glu His Leu Cys Ala Met Thr Gly Val Asp Cys Cys Ile Ser			
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Ser Phe Asp Lys Ser Val Leu Thr Leu Ala Asn Ala Gly Arg Asn Ser			
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Ala Ser Pro Lys His Ser Leu Asn Gly Glu Ser Arg Lys Thr Val Leu			
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Ser Lys Pro Thr Asp Ser Ser Pro Glu Val Ile Asn Tyr Leu Gly Asn			
	1170	1175	1180
Lys Ala Cys Glu Phe Tyr Ile Ser Ile Ala Asp Trp Ala Ala Val Gln			
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Glu Trp Gln Asn Ala Ile His Asp Leu Lys Lys Ser Thr Ser Ser Thr			
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Ser Leu Asn Leu Lys Ala Asp Phe Asn Tyr Ile Lys Ser Leu Ser Ser			
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Ala Thr Ala Leu Asn Pro Ile Glu Gln Asp Gln Lys Trp Gln Ser Ile			
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Thr Glu Asn Val Val Lys Tyr Leu Lys Gln Thr Ser Arg Ile Ala Ile			
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Ala Leu Arg Ser Cys Lys Gln His Asp Val Arg Pro Trp Met Gln Ala			
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Leu Arg Tyr Thr Met Tyr Gln Asn Gln Leu Leu Glu Lys Ile Lys Glu			
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Gln Thr Val Pro Ile Arg Ser His Leu Met Glu Leu Gly Leu Thr Ala			
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Ala Lys Phe Ala Arg Lys Arg Gly Asn Val Ser Leu Ala Thr Arg Leu			
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Leu Ala Gln Cys Ser Glu Val Gln Leu Gly Lys Thr Thr Thr Ala Gln			
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Thr	Ala	Gly	Gln	Ser	Thr	His	Ala	Met	Glu	Met	Leu	Ser	Ser	Cys	Ala	1490	1495	1500
Ile	Ser	Phe	Cys	Lys	Ser	Val	Lys	Ala	Glu	Tyr	Ala	Val	Ala	Lys	Ser	1505	1510	1515
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Asp	Asp	Met	Val	Asp	Val	Ile	Trp	Arg	Gln	Leu	Ile	Ser	Ser	Cys	Pro	1700	1705	1710
Trp	Leu	Ser	Glu	Leu	Asp	Glu	Ser	Ala	Thr	Glu	Gly	Val	Ile	Lys	Val	1715	1720	1725
Trp	Arg	Lys	Val	Val	Asp	Arg	Ile	Phe	Ser	Leu	Tyr	Lys	Leu	Ser	Cys	1730	1735	1740
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Gln	His	Met	Tyr	Val	Leu	Arg	Arg	Ile	Gln	Gln	Leu	Glu	Asp	Glu	Val	
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1985				1990					1995					2000		
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 Phe Arg Met Thr Gln Asn Ile Glu Thr Ala Leu Gly Val Thr Gly Val
 2370 2375 2380
 Glu Gly Val Phe Arg Leu Ser Cys Glu Gln Val Leu His Ile Met Arg
 2385 2390 2395 2400
 Arg Gly Arg Glu Thr Leu Leu Thr Leu Leu Glu Ala Phe Val Tyr Asp
 2405 2410 2415
 Pro Leu Val Asp Trp Thr Ala Gly Gly Glu Ala Gly Phe Ala Gly Ala
 2420 2425 2430
 Val Tyr Gly Gly Gly Gly Gln Gln Ala Glu Ser Lys Gln Ser Lys Arg
 2435 2440 2445
 Glu Met Glu Arg Glu Ile Thr Arg Ser Leu Phe Ser Ser Arg Val Ala
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 Glu Ile Lys Val Asn Trp Phe Lys Asn Arg Asp Glu Met Leu Val Val
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 Leu Pro Lys Leu Asp Gly Ser Leu Asp Glu Tyr Leu Ser Leu Gln Glu
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 Gln Leu Thr Asp Val Glu Lys Leu Gln Gly Lys Leu Leu Glu Glu Ile
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 Gln His Arg Tyr Ser Glu His Thr Gln Leu Gln Thr Gln Gln Arg Ala
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 Val Gln Glu Ala Ile Gln Val Lys Leu Asn Glu Phe Glu Gln Trp Ile
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 Thr His Tyr Gln Ala Ala Phe Asn Asn Leu Glu Ala Thr Gln Leu Ala
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 Ser Leu Leu Gln Glu Ile Ser Thr Gln Met Asp Leu Gly Pro Pro Ser
 2580 2585 2590
 Tyr Val Pro Ala Thr Ala Phe Leu Gln Asn Ala Gly Gln Ala His Leu
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 Ile Ser Gln Cys Glu Gln Leu Glu Gly Glu Val Gly Ala Leu Leu Gln
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 Gln Arg Arg Ser Val Leu Arg Gly Cys Leu Glu Gln Leu His His Tyr
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 Ala Thr Val Ala Leu Gln Tyr Pro Lys Ala Ile Phe Gln Lys His Arg
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 Ile Glu Gln Trp Lys Thr Trp Met Glu Glu Leu Ile Cys Asn Thr Thr
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 Val Glu Arg Cys Gln Glu Leu Tyr Arg Lys Tyr Glu Met Gln Tyr Ala
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 Pro Gln Pro Pro Pro Thr Val Cys Gln Phe Ile Thr Ala Thr Glu Met
 2690 2695 2700
 Thr Leu Gln Arg Tyr Ala Ala Asp Ile Asn Ser Arg Leu Ile Arg Gln
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 Val Glu Arg Leu Lys Gln Glu Ala Val Thr Val Pro Val Cys Glu Asp
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 Gln Leu Lys Glu Ile Glu Arg Cys Ile Lys Val Phe Leu His Glu Asn
 2740 2745 2750
 Gly Glu Glu Gly Ser Leu Ser Leu Ala Ser Val Ile Ile Ser Ala Leu
 2755 2760 2765
 Cys Thr Leu Thr Arg Arg Asn Leu Met Met Glu Gly Ala Ala Ser Ser

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Pro Met Glu Ala Ser Glu Thr Val His Leu Ala Asn Gly Val Tyr Thr		2830
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Ala Leu Arg Cys Leu Met Lys Gly Glu Tyr Thr Leu Glu Ser Met Leu		2860
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Leu His Ala Gln Tyr Gly Glu Leu Ile Gln Pro Arg Asn Gly Ser Val		2925
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Asp Glu Thr Pro Lys Met Ser Ala Gly Gln Met Leu Leu Val Ala Phe		2940
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Asp Gly Met Phe Ala Gln Val Glu Thr Ala Phe Ser Leu Leu Val Glu		2960
	2965	2970
Lys Leu Asn Lys Met Glu Ile Pro Ile Ala Trp Arg Lys Ile Asp Ile		2975
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Gln Met Ala Lys Pro Ile Lys Ala Phe Thr Ala Asp Phe Val Arg Gln		3070
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Ala Val Glu His Asn Ile Gln Ile Gly Lys Phe Ser Gln Leu Val Met		3135
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Asn Arg Ala Thr Val Leu Ala Ser Ser Tyr Asp Thr Ala Trp Lys Lys		3150
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His Asp Leu Val Arg Arg Leu Glu Thr Ser Ile Ser Ser Cys Lys Thr		3165
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Ser Leu Gln Arg Val Gln Leu His Ile Ala Met Phe Gln Trp Gln His		3180
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Glu Asp Leu Leu Ile Asn Arg Pro Gln Ala Met Ser Val Thr Pro Pro		3200
	3205	3210
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 Ser Gln Ile Glu Thr Ser Ile Ala Thr Val Gln Glu Lys Leu Ala Ala
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 Leu Glu Ser Ser Ile Glu Gln Arg Leu Lys Trp Ala Gly Gly Ala Asn
 3250 3255 3260
 Pro Ala Leu Ala Pro Val Leu Gln Asp Phe Glu Ala Thr Ile Ala Glu
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 Arg Arg Asn Leu Val Leu Lys Glu Ser Gln Arg Ala Ser Gln Val Thr
 3285 3290 3295
 Phe Leu Cys Ser Asn Ile Ile His Phe Glu Ser Leu Arg Thr Arg Thr
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 Glu Leu Glu Leu Arg Leu Leu Gln Arg Val Asp Thr Gly Leu Glu His
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 Pro Ile Gly Ser Ser Glu Trp Leu Leu Ser Ala His Lys Gln Leu Thr
 3365 3370 3375
 Gln Asp Met Ser Thr Gln Arg Ala Ile Gln Thr Glu Lys Glu Gln Gln
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