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(54) **METHODS OF IDENTIFYING INSULIN RESPONSE MODULATORS AND USES THEREFOR**

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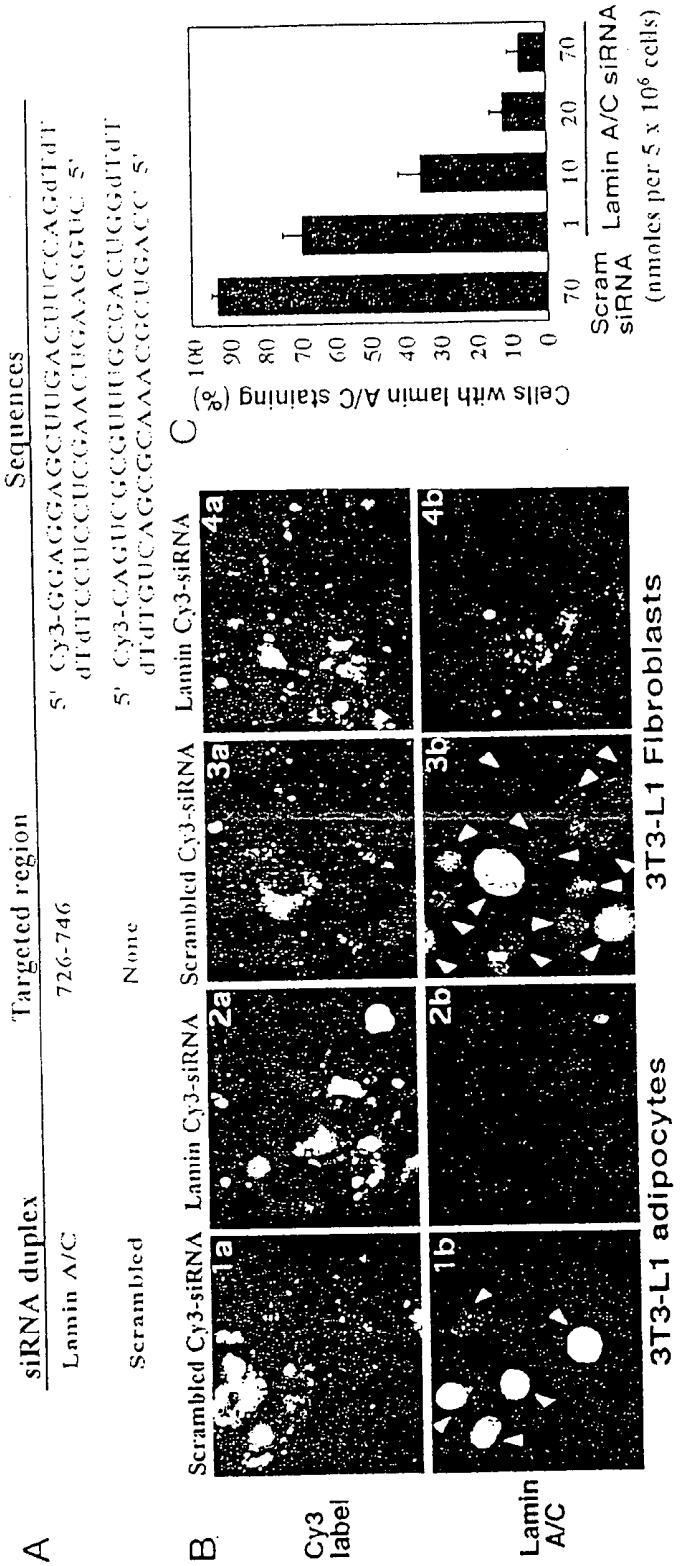
(57) **ABSTRACT**

Methods of identifying insulin response modulators are provided. In particular, methods that feature identifying modulators of Akt and its associated substrates (including R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75), or activities associated therewith, are provided. Therapeutic methods utilizing compounds identified according to the methods of the invention are also provided.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Targeted region
Sequences
Lamin A/C
726-746
5' Cy3-GGAGGAGCUUGACUUCCAGdTdT
dTdTCCUCCGAACUGAAGGUC 5'
Scrambled
None
5' Cy3-CAGUUCGGCGUUUGGCGACUGGGdTdT
dTdTGUCAGCCGCAAACCGCUGACC 5'
B
Scrambled Cy3-siRNA
Lamin Cy3-siRNA
Scrambled Cy3-siRNA
Lamin Cy3-siRNA
1a
2a
3a
4a
1b
2b
3b
4b
Cy3 label
Lamin A/C
3T3-L1 adipocytes
3T3-L1 Fibroblasts
C
Cells with lamin A/C staining (%)
100
90
80
70
60
50
40
30
20
10
0
70
1
10
20
70
Scram siRNA
Lamin A/C siRNA
(nmoles per 5 x 10^6 cells)

FIGURE 1

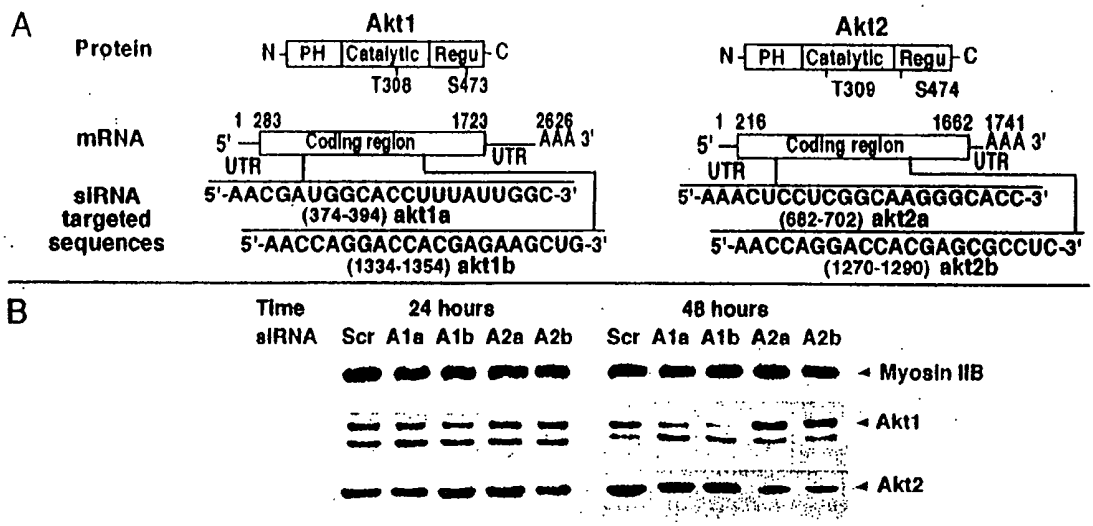
A
Protein
Akt1
N PH Catalytic Regu C
T308 S473
Akt2
N PH Catalytic Regu C
T309 S474
mRNA
1 283 1723 2626
5' Coding region AAA 3'
UTR UTR
1 216 1662 1741
5' Coding region AAA 3'
UTR UTR
siRNA targeted sequences
5'-AACGAUGGCACCUUUAUUGGC-3'
(374-394) akt1a
5'-AACCAGGACCACGAGAAGCUG-3'
(1334-1354) akt1b
5'-AAACUCCUCGGCAAGGGCACC-3'
(682-702) akt2a
5'-AACCAGGACCACGAGCGCCUC-3'
(1270-1290) akt2b
B
Time
siRNA
24 hours
Scr A1a A1b A2a A2b
48 hours
Scr A1a A1b A2a A2b
Myosin IIB
Akt1
Akt2

FIGURE 2

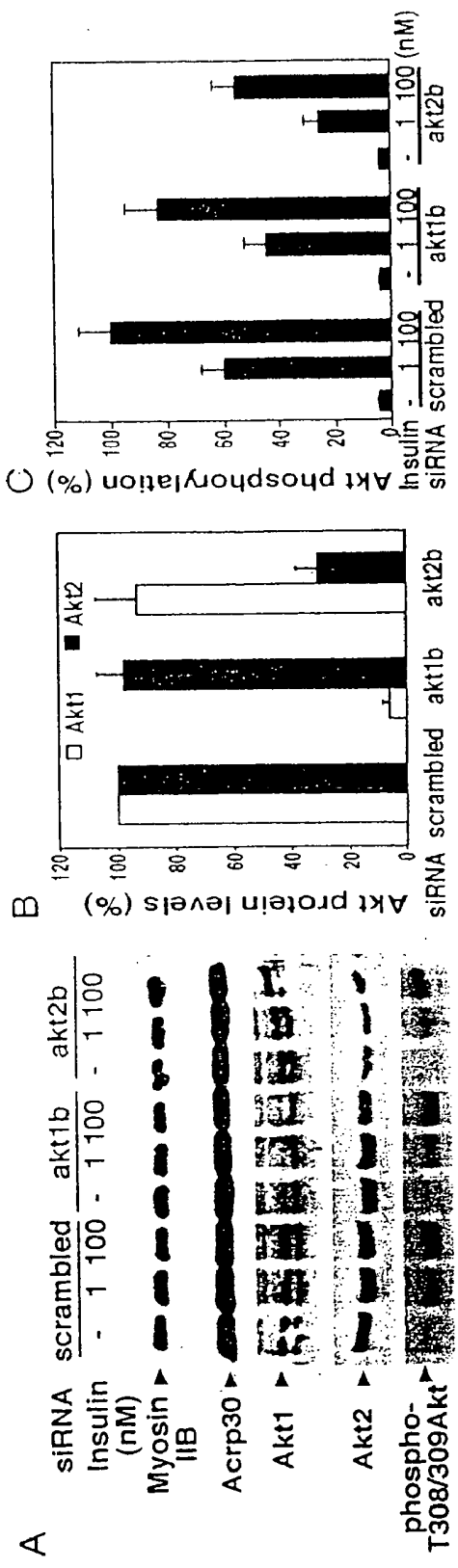
A
siRNA
scrambled
akt1b
akt2b
Insulin (nM)
- 1 100 - 1 100 - 1 100
Myosin IIB
Acrp30
Akt1
Akt2
phospho-T308/309Akt
B
Akt protein levels (%)
Akt1
Akt2
siRNA scrambled akt1b akt2b
C
Akt phosphorylation (%)
Insulin (nM)
- 1 100 - 1 100 - 1 100
siRNA scrambled akt1b akt2b

FIGURE 3

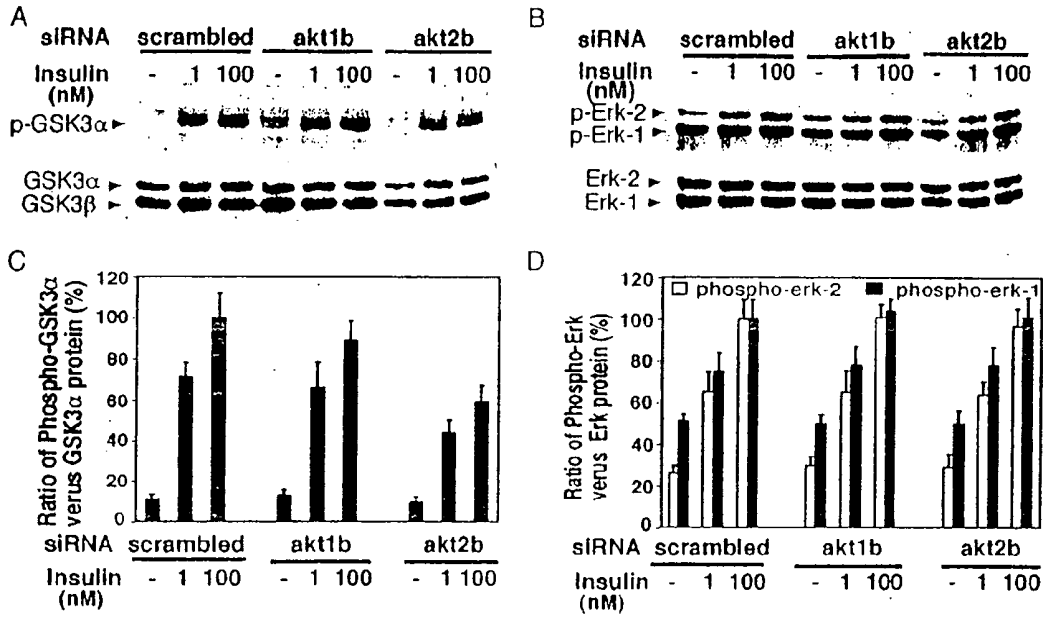
A
siRNA
scrambled
akt1b
akt2b
Insulin (nM)
- 1 100 - 1 100 - 1 100
p-GSK3α
GSK3α
GSK3β
B
siRNA
scrambled
akt1b
akt2b
Insulin (nM)
- 1 100 - 1 100 - 1 100
p-Erk-2
p-Erk-1
Erk-2
Erk-1
C
Ratio of Phospho-GSK3α verus GSK3α protein (%)
120
100
80
60
40
20
0
siRNA scrambled akt1b akt2b
Insulin (nM) - 1 100 - 1 100 - 1 100
D
phospho-erk-2
phospho-erk-1
Ratio of Phospho-Erk verus Erk protein (%)
120
100
80
60
40
20
0
siRNA scrambled akt1b akt2b
Insulin (nM) - 1 100 - 1 100 - 1 100

FIGURE 4

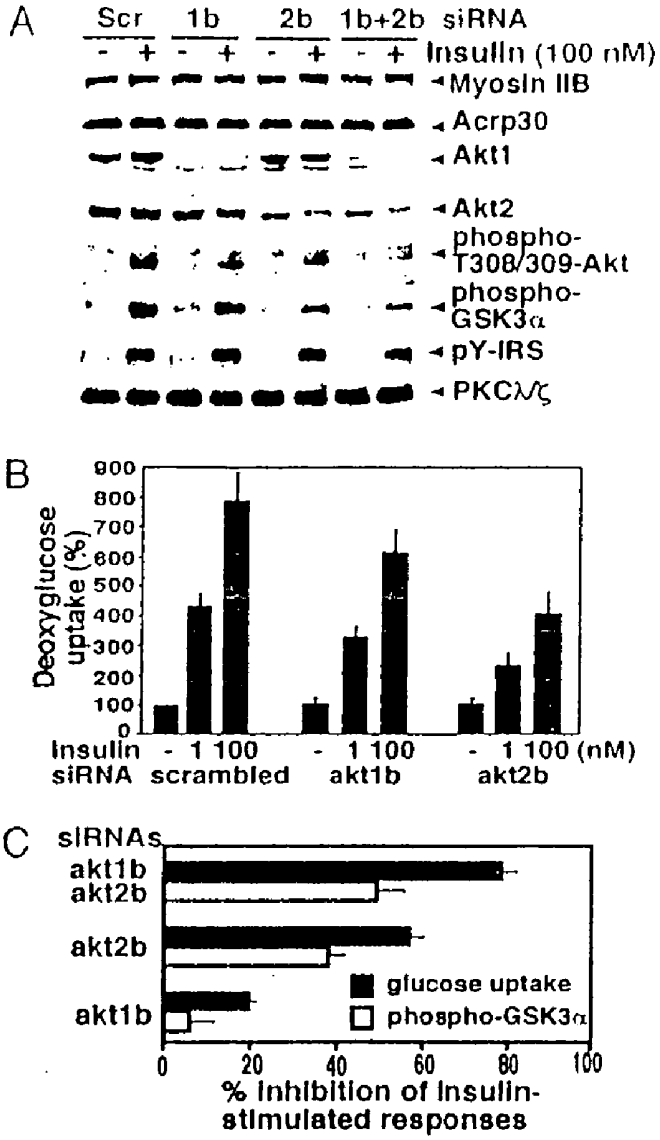
A
Scr
1b
2b
1b+2b
siRNA
- + - + - + - +
Insulin (100 nM)
Myosin IIB
Acrp30
Akt1
Akt2
phospho-T308/309-Akt
phospho-GSK3α
pY-IRS
PKCλ/ζ
B
Deoxyglucose uptake (%)
900
800
700
600
500
400
300
200
100
0
Insulin - 1 100 - 1 100 - 1 100 (nM)
siRNA scrambled akt1b akt2b
C
siRNAs
akt1b
akt2b
akt2b
akt1b
glucose uptake
phospho-GSK3α
0 20 40 60 80 100
% Inhibition of Insulin-stimulated responses

FIGURE 5

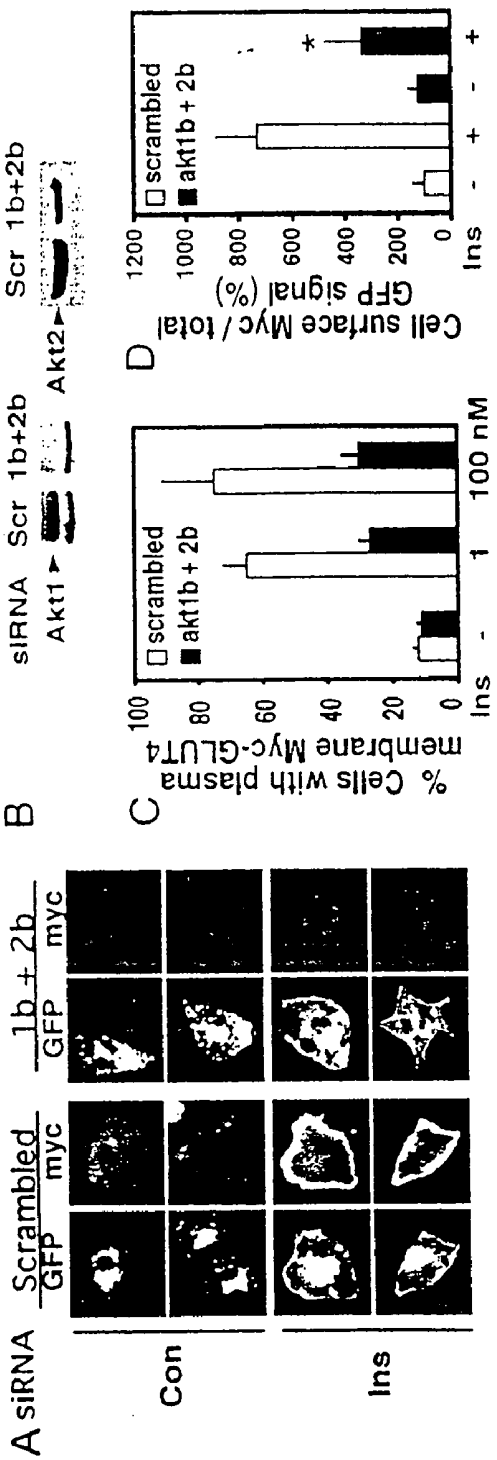
A siRNA
Scrambled
GFP myc
1b + 2b
GFP myc
Con
Ins
B
siRNA Scr 1b+2b Scr 1b+2b
Akt1
Akt2
C
% Cells with plasma membrane Myc-GLUT4
scrambled
akt1b + 2b
Ins - 1 100 nM
D
Cell surface Myc / total GFP signal (%)
scrambled
akt1b + 2b
Ins - + - +

FIGURE 6

METHODS OF IDENTIFYING INSULIN RESPONSE MODULATORS AND USES THEREFOR

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/528,354 filed on Dec. 9, 2003, the contents of which are incorporated herein by reference.

GOVERNMENT RIGHTS

[0002] This invention was made at least in part with government support under Grant No. DK30648 awarded by the National Institutes of Health. The government may have certain rights in this invention.

BACKGROUND OF THE INVENTION

[0003] The regulation of blood glucose levels by insulin is achieved mainly by increased glucose transport exclusively into adipose and skeletal muscle tissue; De Fronzo et al. (1981) *Diabetes* 30:1000-1007 and James et al. (1985) *Am. J. Physiol.* 248:E567-E574. These are the only two tissues that express a specific isoform of the glucose transporter, GLUT4, which mediates the hormonal effect of insulin (for reviews of glucose transporter isoforms and their expression, see Deveskar and Mueckler (1992) *Pediatr. Res.* 31:1-13; Bell et al. (1993) *J. Biol. Chem.* 268:3352-3356; and Baldwin (1993) *Biochim. Biophys. Acta* 1154:17-49). The mechanism of glucose transport activation by insulin is the hormone-dependent enhancement of the rate of GLUT4 translocation from intracellular storage vesicles to the plasma membrane in such a way that the concentration of the transporter on the cell surface increases 10- to 40-fold, depending on the cell type and method of measurement (Zorzono et al. (1989) *J. Biol. Chem.* 264:12358-12363; Holman et al. (1990) *J. Biol. Chem.* 265:18172-18179; Slot et al. (1991) *J. Biol. Chem.* 113:123-135; Slot et al. (1991) *Proc. Nat'l. Acad. Sci. USA* 88:7815-7819; and Smith et al. (1991) *Proc. Nat'l. Acad. Sci. USA* 88:6893-6897). Glucose uptake is increased proportionally to the increment of GLUT4 molecules in the plasma membrane, suggesting that redistribution of transporters is the main, if not only, mechanism that accounts for this effect, Kandror and Pilch (1994) *Proc. Nat'l Acad. Sci USA* 91:8017-8021.

[0004] Insulin signaling through its receptor tyrosine kinase mediates a phosphatidylinositol 3-kinase-dependent pathway that produces the phosphatidylinositol trisphosphate required for recycling GLUT4 to the plasma membrane (Virkamaki et al., (1999) *J. Biol. Chem.* 255:4758-4762; White (2002) *Am. J. Physiol.* 283:E413-E422; Czech et al. (1999) *J. Biol. Chem.* 274:1865-1868). Among the downstream effectors strongly implicated in linking this signaling pathway to components that regulate GLUT4 trafficking is the protein kinase Akt (also known as protein kinase B) based on studies with cultured cells and a gene knockout mouse model (Jiang et al. (2003) *Proc. Natl. Acad. Sci.* 100:7569-7574).

[0005] Akt is present primarily in two isoforms, Akt1 and Akt2. Akt2 is the predominant isoform expressed in muscle and fat. Recent studies demonstrate an important role of both isoforms in glucose homeostasis. Loss of Akt1 alone slightly impairs insulin-mediated hexose transport activity but has no detectable effect on glycogen synthase kinase (GSK)-3 phosphorylation. In contrast, depletion of Akt2 alone by 70% inhibits approximately half of the insulin responsiveness. Combined depletions of Akt1 plus Akt2 in these cells even more markedly attenuated insulin action on glucose transporter 4 movements, hexose transport activity, and GSK-3 phosphorylation. Studies demonstrate a primary role of Akt2 in insulin signaling, significant functional redundancy of Akt1 and Akt2 isoforms in this pathway, and an absolute requirement of Akt protein kinases for regulation of glucose transport and GSK-3 in cultured adipocytes (Jiang et al. (2003) *Proc. Natl. Acad. Sci.* 100:7569-7574).

[0006] Given the important role of Akt in regulating insulin-responsive translocation of GLUT4, understanding the mechanism by which Akt regulates GLUT4 translocation and the substrates that interact with Akt will allow for the identification of modulators for use in regulating a variety insulin-sensitive cellular responses.

SUMMARY OF THE INVENTION

[0007] The present invention is based, at least in part, on the identification of a heretofore unrecognized biological activity of numerous Akt substrates. In particular, the present invention is based on the discovery that these Akt substrates interact with Akt, an important effector molecule implicated in the regulation of GLUT4 trafficking. These Akt substrates were identified by using a proteomics approach and an anti-Akt substrate antibody.

[0008] The present inventors are the first to identify a novel interaction between these Akt substrates and Akt. In particular, the present inventors have demonstrated that these substrates specifically associate with Akt, a critical component of GLUT4 trafficking. Based at least in part on this discovery and on the fact that Akt is important in insulin response and glucose homeostasis, the present invention features methods of identifying insulin response modulators.

[0009] Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **FIG. 1** depicts sequence-specific gene silencing by siRNA transfected into 3T3-L1 fibroblasts and 3T3-L1 adipocytes. **FIG. 1A** depicts sequences of Cy3-labeled lamin A/C and scrambled siRNA duplexes. The lamin A/C sequence is set forth as SEQ ID NO: 1. The scrambled sequence is set forth as SEQ ID NO:2. The **FIG. 1B** depicts the immunofluorescence of nuclear membrane localization of lamin A/C in 3T3-L1 adipocytes and fibroblasts transfected with Cy3-labeled mouse lamin A/C or scrambled siRNA duplexes. **FIG. 1C** depicts concentration dependence of lamin A/C gene silencing by siRNA in 3T3-L1 adipocytes.

[0011] **FIG. 2** depicts time-dependent gene silencing of Akt1 and Akt2 by synthetic siRNA. **FIG. 2A** depicts synthetic siRNA duplexes targeting different regions of Akt1 and Akt2 mRNAs and used for transfection into 3T3-L1 adipocytes. The akt1a sequence is set forth as SEQ ID NO:3. The akt1b sequence is set forth as SEQ ID NO:4. The akt2a sequence is set forth as SEQ ID NO:5. The akt2b sequence is set forth as SEQ ID NO:6. **FIG. 2B** depicts western blots of Akt1, Akt2 and Myosin IIB.

[0012] **FIG. 3** depicts Akt2's primary role in insulin-stimulated Akt protein kinase activity in 3T3-L1 adipocytes.

FIG. 3A depicts 3T3-L1 detection of Akt1, Akt2, phosphoT308/309Akt, Acrp30, Myosin IIB in 3T3-L1 adipocytes transfected with scrambled, akt1b, and akt2b siRNA's. **FIG. 3B** depicts quantification of Akt1 and Akt2 protein levels. **FIG. 3C** depicts quantification of Akt Thr-308/309 phosphorylation.

[**0013**] **FIG. 4** depicts attenuation of insulin-stimulated GSK-3 phosphorylation in 3T3-L1 adipocytes by selective gene silencing. **FIG. 4A** depicts western blot with phosphor-GSK-3 and GSK antibodies. **FIG. 4B** depicts western blot with phosphor-Erk-1/2 and Erk-1/2 antibodies. **FIG. 4C** depicts quantification of phosphorylation of GSK-3α**FIG. 4D** depicts quantification of phosphorylation of Erk-1/2.

[**0014**] **FIG. 5** depicts redundancy of Akt1 and Akt2 in the insulin signaling pathway to hexose transport and GSK-3 phosphorylation in 3T3-L1 adipocytes. **FIG. 5A** depicts western blot images for Akt protein levels, phosphor-Thr-308/309 levels, phosphor-Ser-21-GSK-3α levels, phosphor-Tyr in IRS proteins, and PKCλ/ξ protein levels in total lysates. **FIG. 5B** depicts dose dependence of insulin-stimulated deoxyglucose uptake. **FIG. 5C** depicts inhibition of 100 nM insulin-induced glucose uptake and GSK-3α phosphorylation by knockdown Akt1 and Akt2 protein levels.

[**0015**] **FIG. 6** depicts inhibition of insulin-mediated GLUT4 glucose transporter transduction by combined depletion of Akt1 and Akt2 proteins. **FIG. 6A** depicts representive images for GFP-positive cells and exofacial Myc staining. **FIG. 6B** depicts Akt protein levels in adipocytes transfected with Myc-GLUT4-EGFP and siRNAs for 48 h. **FIG. 6C** depicts percentage of the transfected adipocytes showing a Myc-GLUT4-GFP rim on the cell surface. **FIG. 6D** depicts quantification of the ratio of cell surface Myc signal over the total GFP signal in adipocytes expressing Myc-GLUT4-GFP.

DETAILED DESCRIPTION OF THE INVENTION

[**0016**] The present invention is based, at least in part, on the discovery of previously unrecognized activity of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75). In particular, these proteins have now been discovered to be substrates of Akt. The present invention is based on the discovery of an interaction between these Akt substrates and Akt, an important effector implicated in the regulation of GLUT4 trafficking.

[**0017**] Generally, insulin is a key regulator of glucose homeostasis, and its absence is lethal in humans. The ability of insulin to lower blood glucose stems in part from its actions in muscle and fat to enhance sugar uptake through regulation of GLUT4. These transporters are sequestered in perinuclear membranes in unstimulated cells and are rapidly induced to recycle to the plasma membrane in response to insulin. Insulin signaling through its receptor tyrosine kinase mediates a phosphatidylinositol 3-kinase-dependent pathway that produces the phosphatidylinositol trisphosphate required for recycling GLUT4 to the plasma membrane. Among the downstream effectors strongly implicated in linking this signaling pathway to components that regulate GLUT4 trafficking is the protein kinase Akt (also known as protein kinase B) based on studies with cultured cells and a gene knockout mouse model (Jiang et al. (2003) *Proc. Natl. Acad. Sci.* 100:7569-7574, hereby incorporated by reference).

[**0018**] In accordance with the present invention, the Akt substrates identified herein have been found to associate with Akt and therefore may play an important role in GLUT4 trafficking and, more generally, glucose homeostasis. As such, these Akt substrates provide new targets to modulate insulin effects.

[**0019**] Accordingly, the present invention features methods of identifying insulin response modulators. In certain aspects, the present invention provides methods for identifying an insulin response modulator, including contacting a composition comprising, or a cell that expresses Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate interaction (e.g., binding) of Akt or the Akt bioactive fragment to the Akt substrate or the Akt substrate bioactive fragment, such that the insulin response modulator is identified. In other aspects, the present invention provides methods for identifying an insulin response modulator, including contacting a composition comprising, or a cell that expresses Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate an activity of Akt or the Akt bioactive fragment, such that an the insulin response modulator is identified. In certain embodiments, the activity of Akt or the bioactive fragment thereof may be selected from the group consisting of regulation of insulin signaling to glycogen synthase kinase, regulation of intracellular GLUT4 trafficking and regulation of intracellular retention of GLUT4. In other aspects, the invention provides methods for identifying an insulin response modulator, including contacting a composition comprising, or a cell that expresses Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate an activity of the substrate or the substrate bioactive fragment, such that the insulin response modulator is identified. In further aspects, the invention provides a method for identifying an insulin response modulator, including contacting a composition comprising, or a cell that expresses Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate the phosphorylation state of the Akt substrate or the substrate bioactive fragment, such that the insulin response modulator is identified. In various embodiments of the preceding aspects the modulator identified may be a positive modulator, a negative modulator.

[**0020**] In various embodiments of the preceding aspects of the invention, the Akt substrate may be selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6,

guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75). In other embodiments, the Akt is either Akt1 or Akt2. The Akt bioactive fragment may be any fragment of the Akt substrate having sufficient size and structure to carry out at least one activity (e.g., biological activity) of the corresponding full-length Akt substrate. Exemplary bioactive fragments include, but are not limited to, enzymatic domains, protein binding and/or interaction domains, metal binding domains. Preferred bioactive fragments include regions or domains as described in detail in subsections IA-IQ, infra. The Akt, Akt bioactive fragment, Akt substrate or the substrate bioactive fragment may be detectably labeled, radioactively labeled, or fluorescently labeled. Furthermore, in other embodiments, the interaction, activity, or phosphorylation state may be compared to an appropriate control. In addition, at least one of the Akt, Akt bioactive fragment, Akt substrate or substrate bioactive fragment may be immobilized.

[**0021**] In various embodiments, the activity of the Akt substrate or substrate bioactive fragment is an activity set forth in Table 1 or in subsections IA-IQ, infra. In specific embodiments, the Akt substrate is selected from the group consisting of R-type calcium channel alpha 1E subunit, WNK1, guanine nucleotide exchange factor Lbc (GEF Lbc) or ATP citrate lyase. In yet another embodiment, the Akt substrate is ribosomal protein L6. Bioactive fragments and/or fragment activities (and accordingly, AKT substrate activities) are further described in detail in the references cited throughout subsections IA-IQ, infra. The entire content of these references is incorporated herein by reference.

[**0022**] In the aspects of the present invention where the method involves a cell, the cell may overexpress the Akt substrate or the bioactive fragment thereof, Akt or the bioactive fragment thereof, or both the Akt substrate (or substrate bioactive fragment) and Akt (or Akt bioactive fragment).

[**0023**] In another aspect, the invention provides a modulator as identified by any of the preceding claims. The invention also provides for a pharmaceutical composition including the modulator.

[**0024**] In one aspect, the invention provides a method for identifying an Akt:Akt substrate modulator, including contacting a cell expressing, or a composition comprising, Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to affect interaction (e.g., binding) of the Akt or the bioactive fragment thereof to the Akt substrate or the bioactive fragment thereof, such that the modulator is identified. In another aspect, the invention provides a method for identifying an Akt:Akt substrate modulator, including contacting a cell expressing, or a composition comprising, Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to affect activity of the Akt or the bioactive fragment thereof, such that the modulator is identified. In another aspect, the invention provides a method for identifying an Akt:Akt substrate modulator, including contacting a cell expressing, or a composition comprising, Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to affect activity of the substrate or the bioactive fragment thereof, such that the modulator is identified. In yet another aspect, the invention provides a method for identifying an Akt:Akt substrate modulator, including contacting a cell expressing, or a composition comprising, Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to affect the phosphorylation state of the Akt substrate or the bioactive fragment thereof, such that the modulator is identified.

[**0025**] In certain embodiments of the preceding aspects, the ability of the test compound to affect, for example, interaction activity or phosphorylation; includes the ability of the test compound to either enhance or inhibit such, for example, interaction activity or phosphorylation. The Akt substrate may be selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75). The Akt may be Akt1 or Akt2.

[**0026**] In certain embodiments, the present invention provides methods of modulating insulin responsiveness, regulating glucose transport, regulating gluconeogenesis, regulating glucose homeostasis or regulating blood glucose levels in a subject including administering to the subject an insulin response modulator identified according to the methods of any of the above methods.

[**0027**] In another aspect, the invention provides an antibody that specifically binds to an Akt-interacting domain of an Akt substrate, where the antibody is capable of interfering with the Akt:Akt substrate interaction. The Akt substrate may be selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), or stress 70 protein (p66 mot1/GRP75). The invention further provides for a pharmaceutical composition including the antibody.

[**0028**] In yet another aspect, the present invention provides a pharmaceutical composition including an Akt-interacting domain of an Akt substrate, where the Akt-interacting domain is capable of interfering with the Akt:Akt substrate

interaction. The substrate may be R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (P3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), or stress 70 protein (p66 mot1/GRP75).

[0029] In other aspects, the present invention provides methods for treating an insulin response disease or disorder (e.g., Type I diabetes, Type II diabetes, insulin resistance) including administering any of the pharmaceutical compositions described above.

[0030] Various aspects of the invention are described in further detail in the following subsections:

[0031] I. Substrates:

[0032] According to the invention, several substrates have been identified as interacting with Akt in regulating the insulin response of a cell. These Akt substrates include R-CaC1E, WNK1, FMIP, nGAP-like protein, THO complex 1, HIRIP3, HSP71, ribosomal protein L6, GEF Lbc, ATP citrate lyase, Mi-2b, KIAA0612, AAH07950, pyruvate carboxylase, Eps domain containing protein, nonmuscle myosin IIA (NMMIIA), and p66 mot1/GRP75. Table 1 summarizes the Akt substrates and their putative Akt phosphorylation sites. Using methods described in the present disclosure, use of any one of these substrates in appropriate screening assays would provide for the identification of insulin response modulators.

TABLE 1

Summary of Akt substrates

			Putative Akt Phosphorylation Sites					
GI Acc #	Name	Description	p-site 1	p-site2	p-site3	p-site4	p-site5	psite6
399202	R-CaC1E	R-type calcium channel 1E	T2212	S932	T1059	S934	S2033	S2084
16758634	WNK1	A Serine/Threonine protein kinase	T58 (Akt & pka)	S1884	T1989	T1872	S563 (pkcz)	
24980875	FMIP	Fms interacting protein, interacting with tyrosin kinase receptors	T30	T328				
14009346	nGAP-like protein	similar to Ras GTPase activating protein	S907	S984	T212			
23956332	THO complex 1	protein containing a death domain with unknown function	S9	S240	T259	T153	S504	
21396500	HIRIP3	HIRA interacting protein, may regulate chromatin and histone metabolism	S98	T509	S400	S398		
20820471	HSP71	a heat shock protein	S275 low	T265 low				
16758864	ribosomal protein L6	L6 can be phosphorylated by s6 kinase and recognized by anti-PAS antibody	S72	S141				
15207794	GEF Lbc	Guanine nucleotide exchange factor	S1602	S2237 (pkcz)				
8392839	ATP citrate lyase	Succinyl-CoA synthetase, reported to be AKT substrate	S454	S978	S665 (pkcz)			
4557453	Mi-2b	chromodomain helicase DNA binding protein 4, exist in complex containing deacetylase	S310	multiple PKCz sites				
7513043	KIAA0612	hypothetical protein, similar to peripheral benzodiazapine receptor associated protein 1 and RIM-binding protein 1	S90	S1160	T847			

TABLE 1-continued

Summary of Akt substrates

			Putative Akt Phosphorylation Sites					
GI Acc #	Name	Description	p-site 1	p-site2	p-site3	p-site4	p-site5	psite6
14044052	AAH07950	Similar to heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A)	S193 Low	S154 low				
200246	pyruvate carboxylase		S50					
6677715	Eps domain containing protein	associate with RalBP1	S509	S656	S484			
20137006	NMMIIA	nonmuscle myosin IIA						
6754256	p66 mot1/GRP75	stress 70 protein; dnaK-type chaperone	S662 low	S664 low	T463 low			

[0033] IA. R-type Calcium Channel Alpha-1E Subunit (R-CaC1E)

[0034] R-type Calcium Channel Alpha-1E Subunit (R-CaC1E) has been identified as an Akt substrate that interacts with Akt. Human calcium channel, voltage-dependent, alpha 1E subunit is associated with reference sequence NP_000712 (GenBank Accession No. 4502529). Other relevant sequences include rabbit R-CaC1E (GenBank Accession No. 399202).

NP_000712. calcium channel, voltage-dependent, alpha 1E subunit [gi: 4502529]

LOCUS	NP_000712 2251 aa linear PRI 06-OCT-2003
DEFINITION	calcium channel, voltage-dependent, alpha 1E subunit [*Homo sapiens*].
ACCESSION	NP_000712
VERSION	NP_000712.1 GI: 4502529
DBSOURCE	REFSEQ: accession NM_000721.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 2251)
AUTHORS	Diriong, S., Lory, P., Williams, M. E., Ellis, S. B., Harpold, M. M. and Taviaux, S.
TITLE	Chromosomal localization of the human genes for alpha 1A, alpha 1B, and alpha 1E voltage-dependent Ca2+ channel subunits
JOURNAL	Genomics 30 (3), 605–609 (1995)
MEDLINE	96423049
PUBMED	8825650
REFERENCE	2 (residues 1 to 2251)
AUTHORS	Williams, M. E., Marubio, L. M., Deal, C. R., Hans, M., Brust, P. F., Philipson, L. H., Miller, R. J., Johnson, E. C., Harpold, M. M. and Ellis, S. B.
TITLE	Structure and functional characterization of neuronal alpha 1E calcium channel subtypes
JOURNAL	J. Biol. Chem. 269 (35), 22347–22357 (1994)
MEDLINE	94350992
PUBMED	8071363
REFERENCE	3 (residues 1 to 2251)
AUTHORS	Schneider, T., Wei, X., Olcese, R., Costantin, J. L., Neely, A., Palade, P., Perez-Reyes, E., Qin, N., Zhou, J., Crawford, G. D. et al.
TITLE	Molecular analysis and functional expression of the human type E neuronal Ca2+ channel alpha 1 subunit

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NP_000712. calcium channel, voltage-dependent, alpha 1E subunit [gi: 4502529]

JOURNAL	Recept. Channels 2 (4), 255–270 (1994)
MEDLINE	95236033
PUBMED	7536609
REFERENCE	4 (residues 1 to 2251)
AUTHORS	Soong, T. W., Stea, A., Hodson, C. D., Dubel, S. J., Vincent, S. R. and Snutch, T. P.
TITLE	Structure and functional expression of a member of the low voltage-activated calcium channel family
JOURNAL	Science 260 (5111), 1133–1136 (1993)
MEDLINE	93262464
PUBMED	8388125
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from L29384.1.
FEATURES	Location/Qualifiers
source	1 . . . 2251 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="1" /map="1q25–q31"
Protein	1 . . . 2251 /product="calcium channel, voltage-dependent, alpha 1E subunit"
Region	124 . . . 350 /region_name="Ion transport protein. This family contains Sodium, Potassium, Calcium ion channels. This family is 6 transmembrane helices in which the last two helices flank a loop which determines ion selectivity. In some sub-families (e.g. Na channels) the domain is repeated four times, whereas in others (e.g. K channels) the protein forms as a tetramer in the membrane. A bacterial structure of the protein is known for the last two helices but is not the Pfam family due to it lacking the first four helices" /note="ion_trans" /db_xref="CDD:pfam00520"
Region	523 . . . 701 /region_name="Ion transport protein. This family contains Sodium, Potassium, Calcium ion channels. This family is 6 transmembrane helices in which the last two helices flank a loop which determines ion selectivity. In some sub-families (e.g. Na channels) the domain is repeated four times, whereas in others (e.g. K channels) the protein forms as a tetramer in the membrane. A bacterial structure of the protein is known for the last two helices but is not the Pfam family due to it lacking the first four helices" /note="ion_trans" /db_xref="CDD:pfam00520"
Region	1166 . . . 1366 /region_name="Ion transport protein. This family contains Sodium, Potassium, Calcium ion channels. This family is 6 transmembrane helices in which the last two helices flank a loop which determines ion selectivity. In some sub-families (e.g. Na channels) the domain is repeated four times, whereas in others (e.g. K channels) the protein forms as a tetramer in the membrane. A bacterial structure of the protein is known for the last two helices but is not the Pfam family due to it lacking the first four helices" /note="ion_trans" /db_xref="CDD:pfam00520"
Region	1490 . . . 1703 /region_name="Ion transport protein. This family contains Sodium, Potassium, Calcium ion channels. This family is 6 transmembrane helices in which the last two helices flank a loop which determines ion selectivity. In some sub-families (e.g. Na channels) the domain is repeated four times, whereas in others (e.g. K channels) the protein forms as a tetramer in the membrane. A bacterial

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	NP_000712. calcium channel, voltage-dependent, alpha 1E subunit [gi: 4502529]
	structure of the protein is known for the last two helices but is not the Pfam family due to it lacking the first four helices"
	/note="ion_trans"
	/db_xref="CDD:pfam00520"
variation	2095
	/allele="S"
	/allele="G"
	/db_xref="dbSNP:2480373"
CDS	1 . . . 2251
	/gene="CACNA1E"
	/coded_by="NM_000721.1:166..6921"
	/note="brain specific; go_component: voltage-gated calcium channel complex [goid 0005891] [evidence TAS] [pmid 8071363]; go_component: integral to membrane [goid 0016021] [evidence IEA]; go_function: voltage-gated calcium channel activity [goid 0005245] [evidence TAS] [pmid 8071363]; go_function: calcium ion binding [goid 0005509] [evidence IEA]; go_process: small molecule transport [goid 0006832] [evidence TAS] [pmid 8071363]; go_process: synaptic transmission [goid 0007268] [evidence TAS] [pmid 8071363]; go_process: cation transport [goid 0006812] [evidence IEA]; go_process: calcium ion transport [goid 0006816][evidence IEA]"
	/db_xref="GeneID:777"
	/db_xref="LocusID:777"
	/db_xref="MIM:601013"

[**0035**] Origin

[SEQ ID NO: 7]

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1    marfgeavva rpgsgdgdsd qsrnrqgtpv pasgqaaayk qtkaqrartm alynpipvrq

61   ncftvnrslf ifgednivrk yakklidwpp feymilatii ancivlaleq hlpeddktpm

121  srrlektepy figifcfeag ikivalgfif hkgsylrngw nvmdfivvls gilatagthf

181  nthvdlrtlr avrvlrplkl vsgipslqiv lksimkamvp liqigiliff ailmfaiigl

241  efysgklhra cfmnnsgile gfdpphpcgv qgcpagyeck dwigpndgit qfdnilfavl

301  tvfqcitmeg wttvlyntnd algatwnwly fipliiigsf fvlnlvlgvl sgefakerer

361  venrrafmkl rrqqqierel ngyrawidka eevmlaeenk nagtsalevl rratikrsrt

421  eamtrdssde hcvdissvgt plarasiksa kvdgvsyfrh kerlirisir hmvksqvfyw

481  ivlslvalnt acvaivhhnq pqwlthllyy aeflflglfl lemslkmygm gprlyfhssf

541  ncfdfgvtvg sifevvwaif rpgtsfgisv irairlirif kitkywaslr nlvvslmssm

601  ksiisllfll flfivvfall gmqlfggrfn fndgtpsanf dtfpaaimtv fqiltgedwn

661  evmyngirsq ggvssgmwsa iyfivltlfg nytllnvfla iavdnlanaq eltkdeqeee

721  eafnqkhalq kakevspmsa pnmpsierer rrrhhmsvwe qrtsqlrkhm qmssqealnr

781  eeaptmnpln plnplsslnp lnahpslyrr praieglalg lalekfeeer isrggslkgd

841  ggdrssaldn qrtplslgqr eppwlarpch gncdptqqea gggeavvtfe drarhrqsqr

901  rsrhrrvrte gkesssasrs rsasqersld eamptegekd helrgnhgak eptiqeeraq
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961 dlrrtnslmv srgsglaggl deadtplvlp hpelevgkhv viteqepegs seqallgnvq

1021 ldmgrvisqs epdlscitan tdkattests vtvaipdvdp lvdstvvhis nktdgeaspl

1081 keaeiredee evekkkqkke kretgkamvp hssmfifstt npirrachyi vnlryfemci

1141 llviaassia laaedpvltn sernkvlryf dyvftgvftf emvikmidqg lilqdgsyfr

1201 dlwnildfvv vvgalvafal analgtnkgr diktikslrv lrvlrplkti krlpklkavf

1261 dcvvtslknv fnilivyklf mfifaviavq lfkgkffyct dsskdtekec ignyvdhekn

1321 kmevkgrewk rhefhydnii walltlftvs tgegwpqvlq hsvdvteedr gpsrsnrmem

1381 sifyvvyfvv fpfffvnifv aliiitfqeq gdkmmeecsl ekneracidf aisakpltry

1441 mpqnrhtfqy rvwhfvvsps feytimamia lntvvlmmky ysapctyela lkylniaftm

1501 vfslecvlkv iafgflnyfr dtwnifdfit vigsiteiil tdsklvntsg fnmsflklfr

1561 aarlikllrq gytirillwt fvqsfkalpy vclliamlff iyaiigmqvf gnikldeesh

1621 inrhnnfrsf fgslmllfrs atgeawqeim lsclgekgce pdttapsgqn enercgtdla

1681 yvyfvsfiff csflmlnlfv avimdnfeyl trdssilgph hldefvrvwa eydraacgri

1741 hytemyemlt lmspplglgk rcpskvaykr lvlmnmpvae dmtvhftstl malirtaldi

1801 kiakggadrq qldselqket laiwphlsqk mldllvpmpk asdltvgkiy aammimdyyk

1861 qskvkkqrqq leeqknapmf qrmepsslpq elianakaip ylqqdpvsgl sgrsgypsms

1921 plspqdifql acmdpaddgq fqerqslvvt dpssmrrsfs tirdkrsnss wleefsmers

1981 sentyksrrr syhsslrlsa hrlnsdsghk sdthpsggre rrrskerkhl lspdvsrcns

2041 eergtqadwe sperrqsrsp segrsqtpnr qgtgslsess ipsvsdtstp rrsrrqlppv

2101 ppkprpllsy sslirhagsi sppadgseeg spltsqales nnawltessn sphpqqrqha

2161 spqryisepy lalhedshas dcveeetltf eaavatslgr sntigsappl rhswqmpngh

2221 yrrrrrggpg pgmmcgavnn llsdteeddk c

[0036] IB. WNK1

[0037] WNK1 has been identified as an Akt substrate that interacts with Akt. Human WNK 1 is associated with reference sequence NP_061852 (GenBank Accession No. 12711660). WNK1 is identified and characterized in Verissimo et al. *Oncogene* (2001) 20(39):5562-5569. Other relevant sequences include rat WNK1 associated with reference sequence NP_446246 (GenBank Accession No. 16758634).

NP_061852. protein kinase, 1...[gi: 12711660]

LOCUS	NP_061852 2382 aa linear PRI 05-OCT-2003
DEFINITION	protein kinase, lysine deficient 1; kinase deficient protein [*Homo sapiens*].
ACCESSION	NP_061852
VERSION	NP_061852.1 GI: 12711660
DBSOURCE	REFSEQ: accession NM_018979.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 2382)
AUTHORS	Xu, B. E., Min, X., Stippec, S., Lee, B. H., Goldsmith, E. J. and Cobb, M. H.
TITLE	Regulation of WNK1 by an autoinhibitory domain and autophosphorylation
JOURNAL	J. Biol. Chem. 277 (50), 48456–48462 (2002)
MEDLINE	22359054
PUBMED	12374799

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NP_061852. protein kinase, 1...[gi: 12711660]

REMARK	GeneRIF: identification of autoinhibitory domain
REFERENCE	2
AUTHORS	Verissimo, F. and Jordan, P.
TITLE	WNK kinases, a novel protein kinase subfamily in multi-cellular organisms
JOURNAL	Oncogene 20 (39), 5562–5569 (2001)
MEDLINE	21455683
PUBMED	11571656
REFERENCE	3 (residues 1 to 2382)
AUTHORS	Wilson, F. H., Disse-Nicodeme, S., Choate, K. A., Ishikawa, K., Nelson-Williams, C., Desitter, I., Gunel, M., Milford, D. V., Lipkin, G. W., Achard, J. M., Feely, M. P., Dussol, B., Berland, Y., Unwin, R. J., Mayan, H., Simon, D. B., Farfel, Z., Jeunemaitre, X. and Lifton, R. P.
TITLE	Human hypertension caused by mutations in WNK kinases
JOURNAL	Science 293 (5532), 1107–1112 (2001)
MEDLINE	21390047
PUBMED	11498583
REFERENCE	4 (residues 1 to 2382)
AUTHORS	Moore, T. M., Garg, R., Johnson, C., Coptcoat, M. J., Ridley, A. J. and Morris, J. D.
TITLE	PSK, a novel STE20-like kinase derived from prostatic carcinoma that activates the c-Jun N-terminal kinase mitogen-activated protein kinase pathway and regulates actin cytoskeletal organization
JOURNAL	J. Biol. Chem. 275 (6), 4311–4322 (2000)
MEDLINE	20127920
PUBMED	10660600
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from AJ296290.1. Summary: The WNK1 gene encodes a cytoplasmic serine-threonine kinase expressed in distal nephron.[supplied by OMIM].
FEATURES	Location/Qualifiers
source	1 . . . 2382 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="12" /map="12p13.3"
Protein	1 . . . 2382 /product="protein kinase, lysine deficient 1" /note="kinase deficient protein"
variation	118 /allele="D" /allele="E" /db_xref="dbSNP:11885"
Region	226 . . . 479 /region_name="Serine/Threonine protein kinases, catalytic domain" /note="S_TKc" /db_xref="CDD:smart00220"
variation	531 /allele="N" /allele="D" /db_xref="dbSNP:3178414"
variation	665 /allele="I" /allele="T" /db_xref="dbSNP:2286007"
variation	1056 /allele="P" /allele="T" /db_xref="dbSNP:956868"
variation	1506 /allele="S" /allele="C" /db_xref="dbSNP:7955371"
CDS	1 . . . 2382 /gene="PRKWNK1" /coded_by="NM_018979.1:1..7149" /db_xref="GeneID:65125" /db_xref="LocusID:65125" /db_xref="MIM:605232"

[0038] Origin

[SEQ ID NO: 8]

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1    msggaaekqs stpgslflsp papapkngss sdssvgeklg aaaadavtgr teeyrrrrht

61   mdkdsrgaaa ttttttehrff rrsvicdsna talelpglpl slpqpsipaa vpqsappeph

121  reetvtatat sqvaqgppaa aapgeqavag papstvpsst skdrpvsqps lvgskeeppp

181  arsgsgggsa kepqeersqq qddieeletk avgmsndgrf lkfdieigrg sfktvykgld

241  tettvevawc elqdrkltks erqrfkeeae mlkglqhpni vrfydswest vkgkkcivlv

301  telmtsgtlk tylkrfkvmk ikvlrswcrq ilkglqflht rtppiihrdl kcdnifitgp

361  tgsvkigdlg latlkrasfa ksvigtpefm apemyeekyd esvdvyafgm cmlematsey

421  pysecqnaaq iyrrvtsgvk pasfdkvaip evkeiiegci rqnkderysi kdllnhaffq

481  eetgvrvela eeddgekiai kiwiriedik klkgkykdne aiefsfdler dvpedvaqem

541  vesgyvcegd hktmakaikd rvslikrkre qrqlvreeqe kkkqeesslk qqveqssasq

601  tgikqlpsas tgiptastts asvstqvepe epeadqhqql qyqqpsisvl sdgtvdsgqg

661  ssvftesrvs sqqtvsygsq heqahstgtv pghipstvqa qsqphgvypp ssvaqgqsqg

721  qpsssltgv sssqpiqhpq qqqgiqqtap pqqtvqysls qtstsseatt aqpvsqpqap

781  qvlpqvsagk qlpvsqpvpt iqgepqipva tqpsvvpvhs gahflpvgqp lptpllpqyp

841  vsqipistph vstaqtgfss lpitmaagit qplltlassa ttaaipgvst vvpsqlptll

901  qpvtqlpsqv hpqllqpavq smgipanlgq aaevplssgd vlyqgfpprl ppqypgdsni

961  apssnvasvc ihstvlsppm ptevlatpgy fptvvqpyve snllvpmggv ggqvqvsqpg

1021 gslaqaptts sqqavlestq gvsqvapaep vavaqpqatq pttlassvds ahsdvasgms

1081 dgnenvpsss grhegrttkr hyrksvrsrs rhektsrpkl rilnvsnkgd rvvecqleth

1141 nrkmvtfkfd ldgdnpeeia timvnndfil aieresfvdq vreiiekade mlsedvsvep

1201 egdqgleslq gkddygfsgs qklegefkqp ipassmpqqi giptssltqv vhsagrrfiv

1261 spvpesrlre skvfpseitd tvaastaqsp gmnlshsass lslqqafsel rraqmtegpn

1321 tappnfshtg ptfpvvppfl ssiagvptta aatapvpats sppndistsv iqsevtvpte

1381 egiagvatst gvvtsgglpi ppvsespvls svvssitipa vvsisttsps lqvptstsei

1441 vvsstalyps vtvsatsasa ggstatpgpk ppavvsqqaa gsttvgatlt svstttsfps

1501 tasqlsiqls sststptlae tvvvsahsld ktshssttgl afslsapsss sspgagvssy

1561 isqpgglhpl vipsviastp ilpqaagpts tpllpqvpsi pplvajvanv pavqqtlihs

1621 qpqpallpnq phthcpevds dtqpkapgid diktleeklr slfsehsssg aqhasvslet

1681 slviestvtp gipttavaps klltsttstc lpptnlplgt valpvtpvvt pgqvstpvst

1741 ttsgvkpgta pskppltkap vlpvgtelpa gtlpseqlpp fpgpsltqsq qpledldaql

1801 rrtlspeiit vtsavgpvsm aaptaiteag tqpqkgvsqv kegpvlatss gagvfkmgrf

1861 qvsvaadgaq kegknkseda ksvhfessts essvlssssp estlvkpepn gitipgissd

1921 vpesahktta seaksdtgqp tkvgrfqvtt tankvgrfsv sktedkitdt kkegpvaspp

1981 fmdleqavlp avipkkekpe lsepshlngp ssdpeaafis rdvddgsgsp hsphqlssks

2041 lpsqnlsqsl snsfnssyms sdnesdiede dlklelrrlr dkhlkeiqdl qsrqkheies

2101 lytklgkvpp aviippaapl sgrrrrptks kgskssrsss lgnkspqlsg nlsgqsaasv

2161 lhpqqtlhpp gnipesgqnq llqplkpsps sdnlysafts dgaisvpsls apgqgtsstn
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2221 tvgatvnsqa aqaqppamts srkgtftddl hklvdnward amnlsgrrgs kghmnyegpg

2281 markfsapgq lcismtsnlg gsapisaasa tslghftksm cppqqygfpa tpfgaqwsgt

2341 ggpapqplgq fqpvgtaslq nfnisnlqks isnppgsnlr tt
```

[0039] IC. Fms Interacting Protein (FMIP)

[0040] Fms interacting protein (FMIP) has been identified as an Akt substrate that interacts with Akt. Human FMIP is associated with reference sequence NP_003669 (GenBank Accession No. 19923178). Other relevant sequences include mouse FMIP (GenBank Accession No. 24980875).

NP_003669. Chromosome 22 open reading frame 19 [gi: 19923178]

LOCUS	NP_003669 683 aa linear PRI 05-OCT-2003
DEFINITION	chromosome 22 open reading frame 19; gene from NF2/meningioma region of 22q12 [*Homo sapiens*].
ACCESSION	NP_003669
VERSION	NP_003669.2 GI: 19923178
DBSOURCE	REFSEQ: accession NM_003678.2
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 683)
AUTHORS	Tamura, T., Mancini, A., Joos, H., Koch, A., Hakim, C., Dumanski, J., Weidner, K. M. and Niemann, H.
TITLE	FMIP, a novel Fms-interacting protein, affects granulocyte/macrophage differentiation
JOURNAL	Oncogene 18 (47), 6488–6495 (1999)
MEDLINE	20065119
PUBMED	10597251
REFERENCE	2 (residues 1 to 683)
AUTHORS	Xie, Y. G., Han, F. Y., Peyrard, M., Ruttledge, M. H., Fransson, I., DeJong, P., Collins, J., Dunham, I., Nordenskjold, M. and Dumanski, J. P.
TITLE	Cloning of a novel, anonymous gene from a megabase-range YAC and cosmid contig in the neurofibromatosis type 2/meningioma region on human chromosome 22q12
JOURNAL	Hum. Mol. Genet. 2 (9), 1361–1368 (1993)
MEDLINE	94061029
PUBMED	8242058
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from AB023200.1. On Apr 4. 2002 this sequence version replaced gi: 4505829.
FEATURES	Location/Qualifiers
source	1 . . . 683 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="22" /map="22q12"
Protein	1 . . . 683 /product="chromosome 22 open reading frame 19" /note="gene from NF2/meningioma region of 22q12"
variation	475 /allele="S" /allele="T" /db_xref="dbSNP:8141153"
variation	525 /allele="V" /allele="I" /db_xref="dbSNP:737976"
variation	579 /allele="V" /allele="I" /db_xref="dbSNP:1049534"

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NP_003669. Chromosome 22 open reading frame 19 [gi: 19923178]	
CDS	1 . . . 683 /gene="C22orf19" /coded_by="NM_003678.2:56..2107" /note="go_function: tumor suppressor [goid 0008181] [evidence TAS] [pmid 8242058]" /db_xref="GeneID:8563" /db_xref="LocusID:8563"

[0041] Origin

[SEQ ID NO: 9]

```
1    mssesskkrk pkvirsdgap aegkrnrsdt eqegkyysee aevdlrdpgr dyelykytcq

61   elqrlmaeiq dlksrggkdv aieieerriq scvhfmtlkk inriahirik kgrdqtheak

121  qkvdayhlql qnllyevmhl qkeitkclef kskheeidlv sleefykeap pdiskaevtm

181  gdphqqtlar ldweleqrkr laekyrecls nkekilkeie vkkeylsslq prlnsimqas

241  lpvqeylfmp fdqahkqyet arhlppplyv lfvqataygq acdktlsvai egsvdeakal

301  fkppedsqdd esdsdaeeeq ttkrrrptlg vqlddkrkem lkrhplsvml dlkckddsvl

361  hltfyylmnl nimtvkakvt tamelitpis agdllspdsv lsclypgdhg kktpnpanqy

421  qfdkvgiltl sdyvlelghp ylwvqklggl hfpkeqpqqt viadhslsas hmettmkllk

481  trvqsrlalh kqfaslehgi vpvtsdcqyl fpakvvsrlv kwvtiahedy melhftkdiv

541  daglagdtnl yymaliergt aklqaavvln pgyssippvf qlclnwkgek tnsnddnira

601  megevnvcyk elcgpwpshq lltnqlqrlc vlldvylete shddsvegpk efpqekmclr

661  lfrgpsrmkp fkynhpqgff shr
```

[0042] ID. nGAP-like Protein

[0043] nGAP-like protein has been identified as an Akt substrate that interacts with Akt. Human nGAP-like protein is associated with reference sequence NP_115941 (GenBank Accession No. 20070109). A specific nGAP-like protein sequence is associated with GenBank Accession No. 14009346.

NP_115941. DAB2 interacting protein [gi: 20070109]	
LOCUS	NP_115941 967 aa linear PRI 05-OCT-2003
DEFINITION	DAB2 interacting protein; nGAP-like protein; DOC-2/DAB2 interactive protein [*Homo sapiens*].
ACCESSION	NP_115941
VERSION	NP_115941.1 GI: 20070109
DBSOURCE	REFSEQ: accession NM_032552.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 967)
AUTHORS	Chen, H., Toyooka, S., Gazdar, A. F. and Hsieh, J. T.
TITLE	Epigenetic regulation of a novel tumor suppressor gene (hDAB2IP) in prostate cancer cell lines
JOURNAL	J. Biol. Chem. 278 (5), 3121–3130 (2003)
MEDLINE	22439816
PUBMED	12446720
REMARK	GeneRIF: Epigenetic regulation of this novel tumor suppressor gene in prostate cancer cell lines.

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NP_115941. DAB2 interacting protein [gi: 20070109]

REFERENCE	2 (residues 1 to 967)
AUTHORS	Chen, H., Pong, R. C., Wang, Z. and Hsieh, J. T.
TITLE	Differential regulation of the human gene DAB2IP in normal and malignant prostatic epithelia: cloning and characterization
JOURNAL	Genomics 79 (4), 573–581 (2002)
MEDLINE	21945266
PUBMED	11944990
REMARK	GeneRIF: Normal prostatic epithelial cells have elevated DAB2IP mRNA compared with cancer cells, which correlates with increased DAB2IP promoter activity.
REFERENCE	3 (residues 1 to 967)
AUTHORS	Wang, Z., Tseng, C. P., Pong, R. C., Chen, H., McConnell, J. D., Navone, N. and Hsieh, J. T.
TITLE	The mechanism of growth-inhibitory effect of DOC-2/DAB2 in prostate cancer. Characterization of a novel GTPase-activating protein associated with N-terminal domain of DOC-2/DAB2
JOURNAL	J. Biol. Chem. 277 (15), 12622–12631 (2002)
MEDLINE	21935348
PUBMED	11812785
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from AF367051.1.
FEATURES	Location/Qualifiers
source	1 . . . 967 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="9" /map="9q33.1–q33.3"
Protein	1 . . . 967 /product="DAB2 interacting protein" /note="nGAP-like protein; DOC-2/DAB2 interactive protein"
Region	21 . . . 117 /region_name="Protein kinase C conserved region 2 (CalB)" /note="C2" /db_xref="CDD:smart00239"
Region	143 . . . 456 /region_name="GTPase-activator protein for Ras-like GTPases" /note="RasGAP" /db_xref="CDD:smart00323"
Region	836 . . . 964 /region_name="Chromosome segregation ATPases [Cell division and chromosome partitioning]" /note="Smc" /db_xref="CDD:COG1196"
CDS	1 . . . 967 /gene="DAB2IP" /coded_by="NM_032552.1:306..3209" /note="DIP1/2" /db_xref="GeneID:153090" /db_xref="LocusID:153090"

[0044] Origin

[SEQ ID NO: 10]

```
1    menlrravhp nkdnsrrveh ilklwvieak dlpakkylc elclddvlya rttgklktdn

61   vfwgehfefh nlpplrtvtv hlyretdkkk kkernsylgl vslpaasvag rqfvekwypv

121  vtpnpkggkg pgpmirikar yqtitilpme mykefaehit nhylglcaal epilsaktke

181  emasalvhil qstgkvkdfl tdlmmsevdr cgdnehlifr entlatkaie eylklvgqky

241  lqdalgefik alyesdence vdpskcsaad lpehqgnlkm ccelafckti nsycvfprel

301  kevfaswrqe cssrgrpdis erlisaslfl rflcpaimsp slfnllqeyp ddrtartltl

361  iakvtqnlan fakfgskeey msfmnqfleh ewtnmqrfll eisnpetlsn tagfegyidl

421  grelsslhsl lweavsqleq sivsklgplp rilrdvhtal stpgsgqlpg tndlastpgs
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481  gsssisaglq kmviendlsg lidftrlpsp tpenkdlffv trssgvqpsp arsssysean

541  epdlqmangg kslsmvdlqd artidgeags pagpdvlptd gqaaaaqlva gwparatpvn

601  laglatvrra gqtpttpgts egapgrpqll aplsfqnpvy qmaaglplsp rglgdsgseg

661  hsslsshsns eelaaaaklg sfstaaeela rrpgelarrq msltekggqp tvprqnsagp

721  qrridqpspp ppppppaprg rtppnllstl qyprpssgtl asaspdwvgp strlrqqsss

781  skgdspelkp ravhkqgpsp vspnaldrta awlltmnaql ledeglgpdp phrdrlrskd

841  elsqaekdla vlqdklrist kkleeyetlf kcqeettqkl vleyqarlee geerlrrhee

901  dkdiqmkgii srlmsveeel kkdhaemqaa vdskqkiida qekriaslda anarlmsalt

961  qlkesmh
```

[0045] IE. Nuclear Matrix Protein p84

[0046] Nuclear matrix protein p84 has been identified as an Akt substrate that interacts with Akt. Nuclear matrix protein p84 is associated with reference sequence NP_005122 (GenBank Accession No. 4826882). Other relevant sequences include mouse THO complex 1 associated with reference sequence NP_705780 (GenBank Accession No. 23956332).

NP_005122. nuclear matrix protein p84 [gi: 4826882]

LOCUS	NP_005122 657 aa linear PRI 06-OCT-2003
DEFINITION	nuclear matrix protein p84 [*Homo sapiens*].
ACCESSION	NP_005122
VERSION	NP_005122.1 GI: 4826882
DBSOURCE	REFSEQ: accession NM_005131.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 657)
AUTHORS	Strasser, K., Masuda, S., Mason, P., Pfannstiel, J., Oppizzi, M., Rodriguez-Navarro, S., Rondon, A. G., Aguilera, A., Struhl, K., Reed, R. and Hurt, E.
TITLE	TREX is a conserved complex coupling transcription with messenger RNA export
JOURNAL	Nature 417 (6886), 304–308 (2002)
MEDLINE	22010388
PUBMED	11979277
REFERENCE	2 (residues 1 to 657)
AUTHORS	Durfee, T., Mancini, M. A., Jones, D., Elledge, S. J. and Lee, W. H.
TITLE	The amino-terminal region of the retinoblastoma gene product binds a novel nuclear matrix protein that co-localizes to centers for RNA processing
JOURNAL	J. Cell Biol. 127 (3), 609–622 (1994)
MEDLINE	95050936
PUBMED	7525595
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from L36529.1. Summary: HPR1 is part of the TREX (transcription/export) complex, which includes TEX1 (MIM 606929), THO2 (MM 300395), ALY (MIM 604171), and UAP56 (MM 606390). [supplied by OMIM].
FEATURES	Location/Qualifiers
source	1 . . . 657 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="18" /map="18p11.32"
Protein	1 . . . 657 /product="nuclear matrix protein p84"

-continued

NP_005122. nuclear matrix protein p84 [gi: 4826882]	
Region	561 . . . 652 /region_name="DEATH domain, found in proteins involved in cell death (apoptosis). Alpha-helical domain present in a variety of proteins with apoptotic functions. Some (but not all) of these domains form homotypic and heterotypic dimers" /note="DEATH" /db_xref="CDD:smart00005"
variation	561 /allele="P" /allele="L" /db_xref="dbSNP:7343043"
variation	653 /allele="N" /allele="H" /db_xref="dbSNP:657541"
CDS	1 . . . 657 /gene="THOC1" /coded_by="NM_005131.1:15..1988" /note="go_component: nucleus [goid 0005634] [evidence TAS] [pmid 7525595]; go_process: RNA processing [goid 0006396] [evidence TAS] [pmid 7525595]; go_process: signal transduction [goid 0007165] [evidence IEA]" /db_xref="GeneID:9984" /db_xref="LocusID:9984" /db_xref="MIM:606930"

[**0047**] Origin

[SEQ ID NO: 11]

```
1    msptpplfsl peartrftks trealnnkni kpllstfsqv pgsenekkct ldqafrgile

61   eeiinhssce nvlaiislai ggvtegicta stpfvllgdv ldclpldqcd tiftfveknv

121  atwksntfya agknyllrmc ndllrrlsks qntvfcgriq lflarlfpls eksglnlqsq

181  fnlenvtvfn tneqestlgq khtedreegm dveegemgde eapttcsipi dynlyrkfws

241  lqdyfrnpvq cyekiswktf lkyseevlav fksyklddtq asrkkmeelk tggehvyfak

301  fltseklmdl qlsdsnfrrh illqylilfq ylkgqvkfks snyvltdeqs lwiedttksv

361  yqllsenppd gerfskmveh ilnteenwns wknegcpsfv kertsdtkpt riirkrtape

421  dflgkgptkk iltgneeltr lwnlcpdnme acksetrehm ptleeffeea ieqadpenma

481  eneykamnns nygwralkll arrsphffaj tnqqfkslqe ylenmvikla kelpppseei

541  ktgededeed ndallkenes pdvrrdkpvt geqievfank lgeqwkilap ylemkdseir

601  qiecdsedmk mrakqllvaw qdqegvhatp enlinainks glsdlaeslt ndnetns
```

[0048] IF. HIRA Interacting Protein 3 (HIRIP3)

[0049] HIRA interacting protein 3 (HIRIP3) has been identified as an Akt substrate that interacts with Akt. This protein is associated with reference sequence NP_003600 (GenBank Accession No. 21396500).

NP_003600. HIRA interacting protein 3 [21396500]

LOCUS	NP_003600 556 aa linear PRI 04-OCT-2003
DEFINITION	HIRA interacting protein 3; HIRA-interacting protein 3 [*Homo sapiens*].
ACCESSION	NP_003600
VERSION	NP_003600.2 GI: 21396500
DBSOURCE	REFSEQ: accession NM_003609.2
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 556)
AUTHORS	Lorain, S., Quivy, J. P., Monier-Gavelle, F., Scamps, C., Lecluse, Y., Almouzni, G. and Lipinski, M.
TITLE	Core histones and HIRIP3, a novel histone-binding protein, directly interact with WD repeat protein HIRA
JOURNAL	Mol. Cell. Biol. 18 (9), 5546–5556 (1998)
MEDLINE	98378566
PUBMED	9710638
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AJ223351.2 and BC000588.2. On Jun 12, 2002 this sequence version replaced gi: 5803031. Summary: The HIRA protein shares sequence similarity with Hir1p and Hir2p, the two corepressors of histone gene transcription characterized in the yeast, *Saccharomyces cerevisiae*. The structural features of the HERA protein suggest that it may function as part of a multiprotein complex. Recently, several cDNAs encoding HIRA-interacting proteins, or HIRIPs, have been identified. In vitro, the HIRIP3 gene product binds HIRA, as well as H2B and H3 core histones, indicating that a complex containing HIRA-HIRIP3 could function in some aspects of chromatin and histone metabolism.
FEATURES	Location/Qualifiers
source	1 . . . 556 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="16" /map="16p12.1"
Protein	1 . . . 556 /product="HIRA interacting protein 3" /note="HIRA-interacting protein 3"
CDS	1 . . . 556 /gene="HIRIP3" /coded_by="NM_003609.2:462..2132" /note="go_component: nucleus [goid 0005634] [evidence IEA] [pmid 9710638]; go_process: chromatin assembly/disassembly [goid 0006333] [evidence P] [pmid 9710638]" /db_xref="GeneID:8479" /db_xref="LocusID:8479" /db_xref="MIM:603365"

[0050] Origin

[SEQ ID NO: 12]

```
1    marekemqef trsffrgrpd lstlthsivr rrylahsgrs hlepeekqal krlveeellk

61   mqvdeaasre dkldltkkgk rpptpcsdpe rkrfrfnses esgseasspd yfgppakngv

121  aaevspakee nprraskave essdeerqrd lpaqrgeess eeeekgykgk trkkpvvkkq

181  apgkasvsrk qareeseese aepvqrtakk vegnkgtksl keseqeseee ilaqkkeqre
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241  eeveeeekee deekgdwkpr trsngrrksa reersckqks qakrllgdsd seeeqkeaas

301  sgddsgrdre ppvqrksedr tqlkggkrls gssedeedsg kgeptakgsr kmarlgstsg

361  eesdlerevs dseagggpqg erknrsskks srkgrtrsss sssdgspeak ggkagsgrrg

421  edhpavmrlk ryiracgahr nykkllgscc shkerlsilr aelealgmkg tpslgkcral

481  keqreeaaev asidvanlis gsgrprrrta wnplgeaapp gelyrrtlds deerprpapp

541  dwshmrgiis sdgesn
```

[**0051**] IG. HSP71

[**0052**] Heat shock 70 kDa protein 8 isoform 2 has been identified as an Akt substrate that interacts with Akt. This protein is associated with reference sequence NP_694881 (GenBank Accession No. 24234686). In addition, Heat shock 70 kDa protein 8 isoform 1, associated with reference sequence NP_006588 (GenBank Accession No. 5729877), is identified as an Akt substrate that interacts with Akt. A specific sequence identified as an Akt substrate includes heat shock protein HSP71 (GenBank Accession No. 20820471).

NP_694881. Heat shock 70 kDa protein 8 isoform 2 [gi: 24234686]

LOCUS	NP_694881 493 aa linear PRI 05-OCT-2003
DEFINITION	heat shock 70 kDa protein 8 isoform 2; heat shock cognate protein, 71-kDa; heat shock 70 kd protein 10; heat shock cognate protein 54; constitutive heat shock protein 70; lipopolysaccharide-associated protein 1; LPS-associated protein 1 [*Homo sapiens*].
ACCESSION	NP_694881
VERSION	NP_694881.1 GI: 24234686
DBSOURCE	REFSEQ: accession NM_153201.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 493)
AUTHORS	Shin, B. K., Wang, H., Yim, A. M., Le Naour, F., Brichory, F., Jang, J. H., Zhao, R., Puravs, E., Tra, J., Michael, C. W., Misek, D. E. and Hanash, S. M.
TITLE	Global profiling of the cell surface proteome of cancer cells uncovers an abundance of proteins with chaperone function
JOURNAL	J. Biol. Chem. 278 (9), 7607–7616 (2003)
MEDLINE	22486673
PUBMED	12493773
REFERENCE	2 (residues 1 to 493)
AUTHORS	Noessner, E., Gastpar, R., Milani, V., Brandl, A., Hutzler, P. J., Kuppner, M. C., Roos, M., Kremmer, E., Asea, A., Calderwood, S. K. and Issels, R. D.
TITLE	Tumor-derived heat shock protein 70 peptide complexes are cross-presented by human dendritic cells
JOURNAL	J. Immunol. 169 (10), 5424–5432 (2002)
MEDLINE	22309089
PUBMED	12421917
REMARK	GeneRIF: Tumor-derived HSP70 peptide complexes have the immunogenic potential to instruct dendritic cells to cross-present endogenously expressed, nonmutated, and tumor antigenic peptides shared among tumors of the melanocytic lineage for T cell recognition.
REFERENCE	3 (residues 1 to 493)
AUTHORS	Triantafilou, K., Triantafilou, M. and Dedrick, R. L.
TITLE	A CD14-independent LPS receptor cluster
JOURNAL	Nat. Immunol. 2 (4), 338–345 (2001)
MEDLINE	21174328
PUBMED	11276205
REFERENCE	4 (sites)
AUTHORS	Tsukahara, F., Yoshioka, T. and Muraki, T.
TITLE	Molecular and functional characterization of HSC54, a novel variant of human heat-shock cognate protein 70
JOURNAL	Mol. Pharmacol. 58 (6), 1257–1263 (2000)
MEDLINE	20545701
PUBMED	11093761
REFERENCE	5 (residues 1 to 493)

-continued

NP_694881. Heat shock 70 kDa protein 8 isoform 2 [gi: 24234686]

AUTHORS	Egerton, M., Moritz, R. L., Druker, B., Kelso, A. and Simpson, R. J.
TITLE	Identification of the 70 kD heat shock cognate protein (Hsc70) and alpha-actinin-1 as novel phosphotyrosine-containing proteins in T lymphocytes
JOURNAL	Biochem. Biophys. Res. Commun. 224 (3), 666–674 (1996)
MEDLINE	96311348
PUBMED	8713105
REFERENCE	6 (residues 1 to 493)
AUTHORS	Tavaria, M., Gabriele, T., Anderson, R. L., Mirault, M. E., Baker, E., Sutherland, G. and Kola, I.
TITLE	Localization of the gene encoding the human heat shock cognate protein, HSP73, to chromosome 11
JOURNAL	Genomics 29 (1), 266–268 (1995)
MEDLINE	96079119
PUBMED	8530083
REFERENCE	7 (residues 1 to 493)
AUTHORS	Rensing, S. A. and Maier, U. G.
TITLE	Phylogenetic analysis of the stress-70 protein family
JOURNAL	J. Mol. Evol. 39 (1), 80–86 (1994)
MEDLINE	94343547
PUBMED	7545947
REFERENCE	8 (residues 1 to 493)
AUTHORS	Dworniczak, B. and Mirault, M. E.
TITLE	Structure and expression of a human gene coding for a 71 kd heat shock 'cognate' protein
JOURNAL	Nucleic Acids Res. 15 (13), 5181–5197 (1987)
MEDLINE	87259994
PUBMED	3037489
COMMENT	REVIEWED REFSEO: This record has been curated by NCBI staff. The reference sequence was derived from AB034951.1, AK096100.1 and BC019816.2. Summary: The product encoded by this gene belongs to the heat shock protein 70 family which contains both heat-inducible and constitutively expressed members. The latter are called heat-shock cognate proteins. This gene encodes a heat-shock cognate protein. This protein binds to nascent polypeptides to facilitate correct folding. It also functions as an ATPase in the disassembly of clathrin-coated vesicles during transport of membrane components through the cell. Two alternatively spliced variants have been characterized to date. Transcript Variant: This variant (2) uses an alternate in-frame splice site in the 3' coding region, compared to variant 1, resulting in a shorter protein (isoform 2).
FEATURES	Location/Qualifiers
source	1 . . . 493 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="11" /map="11q24.1"
Protein	1 . . . 493 /product="heat shock 70 kDa protein 8 isoform 2" /note="heat shock cognate protein, 71-kDa; heat shock 70 kd protein 10; heat shock cognate protein 54; constitutive heat shock protein 70; lipopolysaccharide-associated protein 1; LPS-associated protein 1"
Region	6 . . . 462 /region_name="Hsp70 protein. Hsp70 chaperones help to fold many proteins. Hsp70 assisted folding involves repeated cycles of substrate binding and release. Hsp70 activity is ATP dependent. Hsp70 proteins are made up of two regions: the amino terminus is the ATPase domain and the carboxyl terminus is the substrate binding region" /note="HSP70" /db_xref="CDD:pfam00012"

-continued

NP_694881. Heat shock 70 kDa protein 8 isoform 2 [gi: 24234686]	
CDS	1 . . . 493 /gene="HSPA8" /coded_by="NM_153201.1:79..1560" /note="go_component: intracellular [goid 0005622] [evidence NAS] [pmid 8713105]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_function: heat shock protein activity [goid 0003773] [evidence IEA]; go_function: non-chaperonin molecular chaperone ATPase activity [goid 0008571] [evidence NAS] [pmid 8530083]; go_process: protein folding [goid 0006457] [evidence NAS] [pmid 8530083]" /db_xref="GeneID:3312" /db_xref="LocusID:3312" /db_xref="MIM:600816"

[**0053**] Origin

[SEQ ID NO: 13]

```
1    mskgpavgid lgttyscvgv fqhgkveiia ndqgnrttps yvaftdterl igdaaknqva

61   mnptntvfda krligrrfdd avvqsdmkhw pfmvvndagr pkvqveykge tksfypeevs

121  smvltkmkei aeaylgktvt navvtvpayf ndsqrqatkd agtiaglnvl riineptaaa

181  iaygldkkvg aernvlifdl gggtfdvsil tiedgifevk stagdthlgg edfdnrmvnh

241  fiaefkrkhk kdisenkrav rrlrtacera krtlssstqa sieidslyeg idfytsitra

301  rfeelnadlf rgtldpveka lrdakldksq ihdivlvggs tripkiqkll qdffngkeln

361  ksinpdeava ygaavqaail sgdksenvqd lllldvtpls lgietaggvm tvlikrntti

421  ptkqtqtftt ysdnqpgvli qvyegeramt kdnnllgkfe ltgmpggmpg gfpgggapps

481  ggassgptie evd
```

[**0054**]

NP_006588. heat shock 70 kDa protein 8 isoform 1 [gi: 5729877]	
LOCUS	NP_006588 646 aa linear PRI 05-OCT-2003
DEFINITION	heat shock 70 kDa protein 8 isoform 1; heat shock cognate protein, 71-kDa; heat shock 70 kd protein 10; heat shock cognate protein 54; constitutive heat shock protein 70; lipopolysaccharide-associated protein 1; LPS-associated protein 1 [*Homo sapiens*].
ACCESSION	NP_006588
VERSION	NP_006588.1 GI: 5729877
DBSOURCE	REFSEQ: accession NM_006597.3
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 646)
AUTHORS	Shin, B. K., Wang, H., Yim, A. M., Le Naour, F., Brichory, F., Jang, J. H., Zhao, R., Puravs, E., Tra, J., Michael, C. W., Misek, D. E. and Hanash, S. M.
TITLE	Global profiling of the cell surface proteome of cancer cells uncovers an abundance of proteins with chaperone function
JOURNAL	J. Biol. Chem. 278 (9), 7607–7616 (2003)
MEDLINE	22486673
PUBMED	12493773

-continued

NP_006588. heat shock 70 kDa protein 8 isoform 1 [gi: 5729877]

REFERENCE	2 (residues 1 to 646)
AUTHORS	Noessner, E., Gastpar, R., Milani, V., Brandl, A., Hutzler, P. J., Kuppner, M. C., Roos, M., Kremmer, E., Asea, A., Calderwood, S. K. and Issels, R. D.
TITLE	Tumor-derived heat shock protein 70 peptide complexes are cross-presented by human dendritic cells
JOURNAL	J. Immunol. 169 (10), 5424–5432 (2002)
MEDLINE	22309089
PUBMED	12421917
REMARK	GeneRIF: Tumor-derived HSP70 peptide complexes have the immunogenic potential to instruct dendritic cells to cross-present endogenously expressed, nonmutated, and tumor antigenic peptides shared among tumors of the melanocytic lineage for T cell recognition.
REFERENCE	3 (residues 1 to 646)
AUTHORS	Triantafilou, K., Triantafilou, M. and Dedrick, R. L.
TITLE	A CD14-independent LPS receptor cluster
JOURNAL	Nat. Immunol. 2 (4), 338–345 (2001)
MEDLINE	21174328
PUBMED	11276205
REFERENCE	4 (residues 1 to 646)
AUTHORS	Tsukahara, F., Yoshioka, T. and Muraki, T.
TITLE	Molecular and functional characterization of HSC54, a novel variant of human heat-shock cognate protein 70
JOURNAL	Mol. Pharmacol. 58 (6), 1257–1263 (2000)
MEDLINE	20545701
PUBMED	11093761
REFERENCE	5 (residues 1 to 646)
AUTHORS	Egerton, M., Moritz, R. L., Druker, B., Kelso, A. and Simpson, R. J.
TITLE	Identification of the 70 kD heat shock cognate protein (Hsc70) and alpha-actinin-1 as novel phosphotyrosine-containing proteins in T lymphocytes
JOURNAL	Biochem. Biophys. Res. Commun. 224 (3), 666–674 (1996)
MEDLINE	96311348
PUBMED	8713105
REFERENCE	6 (residues 1 to 646)
AUTHORS	Tavaria, M., Gabriele, T., Anderson, R. L., Mirault, M. E., Baker, E., Sutherland, G. and Kola, I.
TITLE	Localization of the gene encoding the human heat shock cognate protein, HSP73, to chromosome 11
JOURNAL	Genomics 29 (1), 266–268 (1995)
MEDLINE	96079119
PUBMED	8530083
REFERENCE	7 (residues 1 to 646)
AUTHORS	Rensing, S. A. and Maier, U. G.
TITLE	Phylogenetic analysis of the stress-70 protein family
JOURNAL	J. Mol. Evol. 39 (1), 80–86 (1994)
MEDLINE	94343547
PUBMED	7545947
REFERENCE	8 (residues 1 to 646)
AUTHORS	Dworniczak, B. and Mirault, M. E.
TITLE	Structure and expression of a human gene coding for a 71 kd heat shock 'cognate' protein
JOURNAL	Nucleic Acids Res. 15 (13), 5181–5197 (1987)
MEDLINE	87259994
PUBMED	3037489
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from BC019816.2 and AK096100.1. Summary: The product encoded by this gene belongs to the heat shock protein 70 family which contains both heat-inducible and constitutively expressed members. The latter are called heat-shock cognate proteins. This gene encodes a heat-shock cognate protein. This protein binds to nascent polypeptides to facilitate correct folding. It also functions as an ATPase in the disassembly of clathrin-coated vesicles during transport of membrane components through the cell. Two alternatively spliced variants have been characterized to date. Transcript Variant: This variant (1) represents the longer transcript and encodes the longer isoform.
FEATURES	Location/Qualifiers
source	1 . . . 646 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="11" /map="11q24.1"

-continued

NP_006588. heat shock 70 kDa protein 8 isoform 1 [gi: 5729877]	
Protein	1 . . . 646 /product="heat shock 70 kDa protein 8 isoform 1" /note="heat shock cognate protein, 71-kDa; heat shock 70 kd protein 10; heat shock cognate protein 54; constitutive heat shock protein 70; lipopolysaccharide-associated protein 1; LPS-associated protein 1"
Region	6 . . . 612 /region_name="Hsp70 protein. Hsp70 chaperones help to fold many proteins. Hsp70 assisted folding involves repeated cycles of substrate binding and release. Hsp70 activity is ATP dependent. Hsp70 proteins are made up of two regions: the amino terminus is the ATPase domain and the carboxyl terminus is the substrate binding region" /note="HSP70" /db_xref="CDD:pfam00012"
CDS	1 . . . 646 /gene="HSPA8" /coded_by="NM_006597.3:79..2019" /note="go_component: intracellular [goid 0005622] [evidence NAS] [pmid 8713105]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_function: heat shock protein activity [goid 0003773] [evidence IEA]; go_function: non-chaperonin molecular chaperone ATPase activity [goid 0008571] [evidence NAS] [pmid 8530083]; go_process: protein folding [goid 0006457] [evidence NAS] [pmid 8530083]" /db_xref="GeneID:3312" /db_xref="LocusID:3312" /db_xref="MIM:600816"

[0055] Origin

[SEQ ID NO: 14]

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  1mskgpavgid  lgttyscvgv  fqhgkveiia  ndqgnrttps  yvaftdterl  igdaaknqva

 61mnptntvfda  krligrrfdd  avvqsdmkhw  pfmvvndagr  pkvqveykge  tksfypeevs

121smvltkmkei  aeaylgktvt  navvtvpayf  ndsqrqatkd  agtiaglnvl  riineptaaa

181iaygldkkvg  aernvlifdl  gggtfdvsil  tiedgifevk  stagdthlgg  edfdnrmvnh

241fiaefkrkhk  kdisenkrav  rrlrtacera  krtlssstqa  sieidslyeg  idfytsitra

301rfeelnadlf  rgtldpveka  lrdakldksq  ihdivlvggs  tripkiqkll  qdffngkeln

361ksinpdeava  ygaavqaail  sgdksenvqd  lllldvtpls  lgietaggvm  tvlikrntti

421ptkqtqtftt  ysdnqpgvli  qvyegeramt  kdnnllgkfe  ltgippaprg  vpqievtfdi

481dangilnvsa  vdkstgkenk  ititndkgrl  skediermvq  eaekykaede  kqrdkvsskn

541slesyafnmk  atvedeklqg  kindedkqki  ldkcneiinw  ldknqtaeke  efehqqkele

601kvcnpiitkl  yqsaggmpgg  mpggfpggga  ppsggassgp  tieevd
```

[0056] IH. Ribosomal Protein L6

[0057] Ribosomal protein L6 has been identified as an Akt substrate that interacts with Akt. This protein is associated with reference sequence NP_000961 (GenBank Accession No. 16753227). Other relevant sequences include rat ribosomal protein L6 associated with reference sequence NP_446423 (GenBank Accession No. 16758864).

NP_000961. Ribosomal protein L6 [gi: 16753227]

LOCUS	NP_000961 288 aa linear PRI 05-OCT-2003
DEFINITION	ribosomal protein L6; 60S ribosomal protein L6; tax-responsive enhancer element-binding protein 107; DNA-binding protein TAXREB107; neoplasm-related protein C140 [*Homo sapiens*].
ACCESSION	NP_000961
VERSION	NP_000961.2 GI: 16753227
DBSOURCE	REFSEQ: accession NM_000970.2
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 288)
AUTHORS	Du, J. P., Jin, X. H., Shi, Y. Q., Cao, Y. X., Zhao, Y. Q., Liu, C. J., Yin, F., Hu, W. H., Chen, B. J., Qiao, T. D. and Fan, D. M.
TITLE	Differential expression of RPL6/Taxreb107 in drug resistant gastric cancer cell line SGC7901/ADR and its correlation with multiple-drug resistance
JOURNAL	Zhonghua Zhong Liu Za Zhi 25 (1), 21–25 (2003)
MEDLINE	22566791
PUBMED	12678981
REMARK	GeneRIF: The high expression of RPL6/Taxreb107 in drug resistant gastric cancer cell shows its correlation with multiple-drug resistance in gastric cancer.
REFERENCE	2 (residues 1 to 288)
AUTHORS	Uechi, T., Tanaka, T. and Kenmochi, N.
TITLE	A complete map of the human ribosomal protein genes: assignment of 80 genes to the cytogenetic map and implications for human disorders
JOURNAL	Genomics 72 (3), 223–230 (2001)
MEDLINE	21295043
PUBMED	11401437
REFERENCE	3 (residues 1 to 288)
AUTHORS	Kenmochi, N., Yoshihama, M., Higa, S. and Tanaka, T.
TITLE	The human ribosomal protein L6 gene in a critical region for Noonan syndrome
JOURNAL	J. Hum. Genet. 45 (5), 290–293 (2000)
MEDLINE	20496216
PUBMED	11043511
REFERENCE	4 (residues 1 to 288)
AUTHORS	Ye, Z. and Connor, J. R.
TITLE	cDNA cloning by amplification of circularized first strand cDNAs reveals non-IRE-regulated iron-responsive mRNAs
JOURNAL	Biochem. Biophys. Res. Commun. 275 (1), 223–227 (2000)
MEDLINE	20403900
PUBMED	10944468
REFERENCE	5 (residues 1 to 288)
AUTHORS	Kenmochi, N., Kawaguchi, T., Rozen, S., Davis, E., Goodman, N., Hudson, T. J., Tanaka, T. and Page, D. C.
TITLE	A map of 75 human ribosomal protein genes
JOURNAL	Genome Res. 8 (5), 509–523 (1998)
MEDLINE	98248690
PUBMED	9582194
REFERENCE	6 (residues 1 to 288)
AUTHORS	Monk, S., Sakuntabhai, A., Carter, S. A., Bryce, S. D., Cox, R., Harrington, L., Levy, E., Ruiz-Perez, V. L., Katsantoni, E., Kodvawala, A., Munro, C. S., Burge, S., Larregue, M., Nagy, G., Rees, J. L., Lathrop, M., Monaco, A. P., Strachan, T. and Hovnanian, A.
TITLE	Refined genetic mapping of the darier locus to a <1-cM region of chromosome 12q24.1, and construction of a complete, high-resolution P1 artificial chromosome/bacterial artificial chromosome contig of the critical region
JOURNAL	Am. J. Hum. Genet. 62 (4), 890–903 (1998)
MEDLINE	98198349
PUBMED	9529352
REFERENCE	7 (residues 1 to 288)
AUTHORS	Wool, I. G., Chan, Y. L. and Gluck, A.
TITLE	Structure and evolution of mammalian ribosomal proteins
JOURNAL	Biochem. Cell Biol. 73 (11–12), 933–947 (1995)
MEDLINE	96282697
PUBMED	8722009
REMARK	This review focuses primarily on rat ribosomal proteins, but it compares them to human ribosomal proteins.

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NP_000961. Ribosomal protein L6 [gi: 16753227]

REFERENCE	8 (residues 1 to 288)
AUTHORS	Ohta, K., Endo, T., Gunji, K. and Onaya, T.
TITLE	Isolation of a cDNA whose expression is markedly increased in malignantly transformed FRTL cells and neoplastic human thyroid tissues
JOURNAL	J. Mol. Endocrinol. 12 (1), 85–92 (1994)
MEDLINE	94242236
PUBMED	8185817
REFERENCE	9 (residues 1 to 288)
AUTHORS	Zaman, G. J.
TITLE	Sequence of a cDNA encoding human ribosomal protein L26 and of a cDNA probably encoding human ribosomal protein L6
JOURNAL	Nucleic Acids Res. 21 (7), 1673 (1993)
MEDLINE	93241958
PUBMED	8479925
REFERENCE	10 (residues 1 to 288)
AUTHORS	Morita, T., Sato, T., Nyunoya, H., Tsujimoto, A., Takahara, J., Irino, S. and Shimotohno, K.
TITLE	Isolation of a cDNA clone encoding DNA-binding protein (TAXREB107) that binds specifically to domain C of the tax-responsive enhancer element in the long terminal repeat of human T-cell leukemia virus type I
JOURNAL	AIDS Res. Hum. Retroviruses 9 (2), 115–121 (1993)
MEDLINE	93207816
PUBMED	8457378
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from BC004138.2. On Nov 6, 2001 this sequence version replaced gi: 4506657. Summary: Ribosomes, the organelles that catalyze protein synthesis, consist of a small 40S subunit and a large 60S subunit. Together these subunits are composed of 4 RNA species and approximately 80 structurally distinct proteins. This gene encodes a ribosomal protein that is a component of the 60S subunit. The protein belongs to the L6E family of ribosomal proteins. It is located in the cytoplasm. The protein can bind specifically to domain C of the tax-responsive enhancer element of human T-cell leukemia virus type 1, and it has been suggested that the protein may participate in tax-mediated transactivation of transcription. As is typical for genes encoding ribosomal proteins, there are multiple processed pseudogenes of this gene dispersed through the genome.
FEATURES	Location/Qualifiers
source	1 . . . 288 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="12" /map="12q24.1"
Protein	1 . . . 288 /product="ribosomal protein L6" /note="60S ribosomal protein L6; tax-responsive enhancer element-binding protein 107; DNA-binding protein TAXREB107; neoplasm-related protein C140"
Region	42 . . . 72 /region_name="Ribosomal protein L6, N-terminal domain" /note="Ribosomal_L6e_N" /db_xref="CDD:pfam03868"
variation	123 /allele="P" /allele="R" /db_xref="dbSNP:3933539"
Region	181 . . . 288 /region_name="Ribosomal protein L6e" /note="Ribosomal_L6e" /db_xref="CDD:pfam01159"
variation	245 /allele="Q" /allele="R" /db_xref="dbSNP:15146"
CDS	1 . . . 288 /gene="RPL6" /coded_by="NM_000970.2:32..898" /note="go_component: cytosolic large ribosomal subunit (sensu Eukarya) [goid 0005842] [evidence TAS] [pmid 8479925];"

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NP_000961. Ribosomal protein L6 [gi: 16753227]
go_component: ribosome [goid 0005840] [evidence IEA]; go_component: intracellular [goid 0005622] [evidence IEA]; go_function: structural protein of ribosome [goid 0003735] [evidence P] [pmid 8479925]; go_function: RNA binding [goid 0003723] [evidence TAS] [pmid 8479925]; go_function: DNA binding [goid 0003677] [evidence TAS] [pmid 8457378]; go_function: structural constituent of ribosome [goid 0003735] [evidence TAS] [pmid 8479925]; go_process: regulation of transcription, DNA-dependent [goid 0006355] [evidence TAS] [pmid 8457378]; go_process: protein biosynthesis [goid 0006412] [evidence TAS] [pmid 8479925]" /db_xref="GeneID:6128" /db_xref="LocusID:6128" /db_xref="MIM:603703"

[**0058**] Origin

[SEQ ID NO: 15]

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121vprkllshgk  kpfsqhvrkl  rasitpgtil  iiltgrhrgk  rvvflkqlas  glllvtgplv

181lnrvplrrth  qkfviatstk  idisnvkipk  hltdayfkkk  klrkprhqeg  eifdtekeky

241eiteqrkidq  kavdsqilpk  ikaipqlqgy  lrsvfaltng  iyphklvf
```

[**0059**] II. Guanine Nucleotide Exchange Factor Lbc (GEF Lbc)

[**0060**] A-kinase anchor protein 13 isoform 2 (A-kinase anchoring protein; guanine nucleotide exchange factor Lbc (GEF Lbc) has been identified as an Akt substrate that interacts with Akt. This protein is associated with reference sequence NP_009131 (GenBank Accession No. 21493029). In addition, A-kinase anchor protein 13 isoform 1, associated with reference sequence NP_006729 (GenBank Accession No. 31563330), and A-kinase anchor protein 13 isoform 3, associated with reference sequence NP_658913 (GenBank Accession No. 21493031), are identified as Akt substrates that interact with Akt. A specific sequence identified as an Akt substrate includes Guanine Nucleotide Exchange Factor Lbc (GEF Lbc) (GenBank Accession No. 15207794).

NP_009131. A-kinase anchor protein 13 isoform 2 [gi: 21493029]	
LOCUS	NP_009131 2813 aa linear PRI 05-OCT-2003
DEFINITION	A-kinase anchor protein 13 isoform 2; A-kinase anchoring protein; guanine nucleotide exchange factor Lbc; breast cancer nuclear receptor-binding auxiliary protein; lymphoid blast crisis oncogene [*Homo sapiens*].
ACCESSION	NP_009131
VERSION	NP_009131.2 GI: 21493029
DBSOURCE	REFSEQ: accession NM_007200.3
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 2813)
AUTHORS	Spierings, E., Brickner, A. G., Caldwell, J. A., Zegveld, S., Tatsis, N., Blokland, E., Pool, J., Pierce, R. A., Mollah, S., Shabanowitz, J., Eisenlohr, L. C., van Veelen, P., Ossendorp, F., Hunt, D. F., Goulmy, E. and Engelhard, V. H.
TITLE	The minor histocompatibility antigen HA-3 arises from differential proteasome-mediated cleavage of the lymphoid blast crisis (Lbc) oncoprotein

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NP_009131. A-kinase anchor protein 13 isoform 2 [gi: 21493029]

JOURNAL	Blood 102 (2), 621–629 (2003)
MEDLINE	22718699
PUBMED	12663445
REMARK	GeneRIF: The HA-3 peptide, VTEPGTAQY, is encoded by the lymphoid blast crisis oncogene, showing for the 1st time that a leukemia-associated oncogene can give rise to immunogenic T-cell epitopes that may participate in antihost & antileukemic alloimmune responses.
REFERENCE	2 (residues 1 to 2813)
AUTHORS	Park, B., Nguyen, N. T., Dutt, P., Merdek, K. D., Bashar, M., Sterpetti, P., Tosolini, A., Testa, J. R. and Toksoz, D.
TITLE	Association of Lbc Rho guanine nucleotide exchange factor with alpha-catenin-related protein, alpha-catulin/CTNNAL1, supports serum response factor activation
JOURNAL	J. Biol. Chem. 277 (47), 45361–45370 (2002)
MEDLINE	22323310
PUBMED	12270917
REMARK	GeneRIF: Results show that alpha-catulin co-expression leads to increased Lbc-induced serum response factor activation and may modulate Rho pathway signaling in vivo by providing a scaffold for the Lbc Rho guanine nucleotide exchange factor.
REFERENCE	3 (residues 1 to 2813)
AUTHORS	Diviani, D., Soderling, J. and Scott, J. D.
TITLE	AKAP-Lbc anchors protein kinase A and nucleates Galpha 12-selective Rho-mediated stress fiber formation
JOURNAL	J. Biol. Chem. 276 (47), 44247–44257 (2001)
MEDLINE	21570178
PUBMED	11546812
REFERENCE	4 (residues 1 to 2813)
AUTHORS	Klussmann, E., Edemir, B., Pepperle, B., Tamma, G., Henn, V., Klauschenz, E., Hundsrucker, C., Maric, K. and Rosenthal, W.
TITLE	Ht31: the first protein kinase A anchoring protein to integrate protein kinase A and Rho signaling
JOURNAL	FEBS Lett. 507 (3), 264–268 (2001)
MEDLINE	21553155
PUBMED	11696353
REFERENCE	5 (residues 1 to 2813)
AUTHORS	Sterpetti, P., Hack, A. A., Bashar, M. P., Park, B., Cheng, S. D., Knoll, J. H., Urano, T., Feig, L. A. and Toksoz, D.
TITLE	Activation of the Lbc Rho exchange factor proto-oncogene by truncation of an extended C terminus that regulates transformation and targeting
JOURNAL	Mol. Cell. Biol. 19 (2), 1334–1345 (1999)
MEDLINE	99108106
PUBMED	9891067
REFERENCE	6 (residues 1 to 2813)
AUTHORS	Rubino, D., Driggers, P., Arbit, D., Kemp, L., Miller, B., Coso, O., Pagliai, K., Gray, K., Gutkind, S. and Segars, J.
TITLE	Characterization of Brx, a novel Dbl family member that modulates estrogen receptor action
JOURNAL	Oncogene 16 (19), 2513–2526 (1998)
MEDLINE	98288806
PUBMED	9627117
REFERENCE	7 (residues 1 to 2813)
AUTHORS	Toksoz, D. and Williams, D. A.
TITLE	Novel human oncogene lbc detected by transfection with distinct homology regions to signal transduction products
JOURNAL	Oncogene 9 (2), 621–628 (1994)
MEDLINE	94119604
PUBMED	8290273
REFERENCE	8 (residues 1 to 2813)
AUTHORS	Carr, D. W., Hausken, Z. E., Fraser, I. D., Stofko-Hahn, R. E. and Scott, J. D.
TITLE	Association of the type II cAMP-dependent protein kinase with a human thyroid RII-anchoring protein. Cloning and characterization of the RII-binding domain
JOURNAL	J. Biol. Chem. 267 (19), 13376–13382 (1992)
MEDLINE	92317056
PUBMED	1618839
REFERENCE	9 (residues 1 to 2813)
AUTHORS	Carr, D. W., Stofko-Hahn, R. E., Fraser, I. D., Bishop, S. M., Acott, T. S., Brennan, R. G. and Scott, J. D.

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NP_009131. A-kinase anchor protein 13 isoform 2 [gi: 21493029]

TITLE	Interaction of the regulatory subunit (RII) of cAMP-dependent protein kinase with RII-anchoring proteins occurs through an amphipathic helix binding motif
JOURNAL	J. Biol. Chem. 266 (22), 14188–14192 (1991)
MEDLINE	91317762
PUBMED	1860836
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AB055890.1, AK091210.1, AL135297.1 and BC050312.1. On Jun 20, 2002 this sequence version replaced gi: 17933492. Summary: The A-kinase anchor proteins (AKAPs) are a group of structurally diverse proteins, which have the common function of binding to the regulatory subunit of protein kinase A (PKA) and confining the holoenzyme to discrete locations within the cell. This gene encodes a member of the AKAP family. Alternative splicing of this gene results in at least 3 transcript variants encoding different isoforms containing a dbl oncogene homology (DH) domain and a pleckstrin homology (PH) domain. The DH domain is associated with guanine nucleotide exchange activation for the Rho/Rac family of small GTP binding proteins, resulting in the conversion of the inactive GTPase to the active form capable of transducing signals. The PH domain has multiple functions. Therefore, these isoforms function as scaffolding proteins to coordinate a Rho signaling pathway and, in addition, function as protein kinase A-anchoring proteins. Transcript Variant: This variant (2) contains an internal alternate in-frame exon in the coding region, as compared to variant 1. Isoform 2 differs from isoform 1 in a small middle region.
FEATURES	Location/Qualifiers
source	1 . . . 2813 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="15" /map="15q24–q25"
Protein	1 . . . 2813 /product="A-kinase anchor protein 13 isoform 2" /note="A-kinase anchoring protein; guanine nucleotide exchange factor Lbc; breast cancer nuclear receptor-binding auxiliary protein; lymphoid blast crisis oncogene"
Region	166 . . . 224 /region_name="ankyrin repeats"
variation	452 /allele="T" /allele="M" /db_xref="dbSNP:2061821"
variation	494 /allele="W" /allele="R" /db_xref="dbSNP:2061822"
variation	574 /allele="R" /allele="C" /db_xref="dbSNP:2061824"
variation	624 /allele="V" /allele="G" /db_xref="dbSNP:745191"
variation	689 /allele="K" /allele="E" /db_xref="dbSNP:7177107"
variation	845 /allele="V" /allele="A" /db_xref="dbSNP:4075256"
variation	897 /allele="V" /allele="M" /db_xref="dbSNP:4075254"
variation	1062 /allele="P" /allele="A" /db_xref="dbSNP:4843074"

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NP_009131. A-kinase anchor protein 13 isoform 2 [gi: 21493029]

variation	1086 /allele="N" /allele="D" /db_xref="dbSNP:4843075"
variation	1216 /allele="T" /allele="M" /db_xref="dbSNP:7162168"
Region	1788 . . . 1826 /region name="C1 homology region"
Region	1998 . . . 2189 /region_name="Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases" /note="RhoGEF" /db_xref="CDD:smart00325"
variation	2179 /allele="N" /allele="S" /db_xref="dbSNP:3743323"
variation	2457 /allele="G" /allele="S" /db_xref="dbSNP:2241268"
variation	2801 /allele="A" /allele="T" /db_xref="dbSNP:2614668"
CDS	1 . . . 2813 /gene="AKAP13" /coded_by="NM_007200.3:171..8612" /note="go component: membrane fraction [goid 0005624] [evidence E]; go function: protein kinase A anchoring activity [goid 0005079] [evidence E] [pmid 1618839]; go_function: protein binding [goid 0005515] [evidence E] [pmid 1860836]; go_function: Rho guanyl-nucleotide exchange factor activity [goid 0005089] [evidence NR]; go_function: signal transducer activity [goid 0004871] [evidence P]; go_process: oncogenesis [goid 0007048] [evidence P]; go_process: signal transduction [goid 0007165] [evidence NR]" /db_xref="GeneID:11214" /db_xref="LocusID:11214" /db_xref="MIM:604686"

[**0061**] Origin

[SEQ ID NO: 16]

```
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 121 qsgppsgdvn  sldkklvlaf  rhikiptewn  vlgtdqslhd  agpretlmhf  avrlgllrlt

 181 wfllqkpggr   galsihnqeg  atpvslaler  gyhklhqllt  eenagepdsw  sslsyeipyg

 241 dcsvrhhrel  diytltsesd  shhehpfpgd  gctgpifklm  niqqqlmktn  lkqmdslmpl

 301 mmtaqdpssa  petdgqflpc   apeptdpqrl  ssseetestq  ccpgspvaqt  espcdlssiv

 361 eeentdrscr  kknkgverkg  eevepapivd  sgtvsdqdsc  lqslpdcgvk  gteglsscgn

 421 rneetgtkss  gmptdqesls  sgdavlqrdl  vmepgtaqys  sggelggist  tnvstpdtag

 481 emehglmnpd  atvwknvlqg  gestkerfen  snigtagasd  vhvtskpvdk  isvpncapaa

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601 lepytllaag igeamspsdl allgleedvm phqnsetnss haqsqkgkss picsttgddk

661 lcadsacqqn tvtssgdlva klcdnivses esttarqpss qdppdashce dpqahtvtsd

721 pvrdtqerad fcpfkvvdnk gqrkdvkldk pltnmlevvs hphpvvpkme kelvpdqavi

781 sdstfslans pgsesvtkdd alsfvpsqke kgtatpelht atdyrdgpdg nsnepdtrpl

841 edravglsts staaelqhgm gntsltglgg ehegpappai pealnikgnt dsslqsvgka

901 tlaldsvlte egkllvvses saaqeqdkdk avtcssiken alssgtlqee qrtpppgqdt

961 qqfheksisa dcakdkalql snspgassaf lkaetehnke vapqvslltq ggaaqslvpp

1021 gaslatesrq ealgaehnss allpcllpdg sdgsdalncs qpspldvgvk ntqsqgktsa

1081 cevsgdvtvd vtgvnalqgm aeprrenish ntqdilipnv llsqeknavl glpvalqdka

1141 vtdpqgvgtp emipldwekg klegadhsct mgdaeeaqid deahpvllqp vakelptdme

1201 lsahddgapa gvrevmrapp sgrerstpsl pcmvsaqdap lpkgadliee aasrivdavi

1261 eqvkaagall tegeachmsl sspelgpltk glesaftekv stfppgeslp mgstpeeatg

1321 slagcfagre epekiilpvq gpepaaempd vkaedevdfr assiseevav gsiaatlkmk

1381 qgpmtqainr enwctiepcp daasllaskq specenfldv glgrectskq gvlkresgsd

1441 sdlfhspsdd mdsiifpkpe eehlacditg sssstddtas ldrhsshgsd vslsqilkpn

1501 rsrdrqsldg fyshgmgaeg resesepadp gdveeeemds itevpancsv lrssmrslsp

1561 frrhswgpgk naasdaemnh rssmrvlgdv vrrppihrrs fslegltgga gvgnkpsssl

1621 evssanaeel rhpfsgeerv dslvslseed lesdqrehrm fdqqichrsk qqgfnyctsa

1681 isspltksis lmtishpgld nsrpfhstfh ntsanltesi teenynfiph spskkdsewk

1741 sgtkvsrtfs yiknkmsssk kskekekekd kikekekdsk dkekdkktvn ghtfssipvv

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1861 vimrnkpsqp kerprsavll vdetattpif anrrsqqsvs lsksvsiqni tgvgndenms

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1981 dskflkqqkk dvvkrqeviy elmqtefhhv rtlkimsgvy sqgmmadllf eqqmveklfp

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2281 islkklivre vaheekglfl ismgmtdpem vevhasskee rnswiqiiqd tintlnrded

2341 egipseneee kkmldtrare lkeqlhqkdq killileeke mifrdmaecs tplpedcspt

2401 hsprvlfrsn teealkggpl mksainevei lqglvsgnlg gtlgptvssp ieqdvvgpvs

2461 lprraetfgg fdshqmnask ggekeegddg qdlrrtesds glkkggnanl vfmlkrnseq

2521 vvqsvvhlye llsalqgvvl qqdsyiedqk lvlseraltr slsrpsslie qekqrslekq

2582 rqdlanlqkq qaqyleekrr rerewearer elrerealla qreeevqqgq qdlekereel

2641 qqkkgtyqyd lerlraaqkq lereqeqlrr eaerlsqrqt erdlcqvshp htklmripsf

2701 fpspeeppsp sapsiaksgs ldselsvspk rnsisrthkd kgpfhilsst sqtnkgpegq

2761 sqapastsas trlfgltkpk ekkekkkknk tsrsqpgdgp asevsaegee ifc

[0062]

NP_006729. A kinase anchor protein 13 isoform 1 [gi: 31563330]

LOCUS	NP_006729 2817 aa linear PRI 05-OCT-2003
DEFINITION	A-kinase anchor protein 13 isoform 1; A-kinase anchoring protein; guanine nucleotide exchange factor Lbc; breast cancer nuclear receptor-binding auxiliary protein; lymphoid blast crisis oncogene [*Homo sapiens*].
ACCESSION	NP_006729
VERSION	NP_006729.4 GI: 31563330
DBSOURCE	REFSEQ: accession NM 006738.4
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 2817)
AUTHORS	Spierings, E., Brickner, A. G., Caldwell, J. A., Zegveld, S., Tatsis, N., Blokland, E., Pool, J., Pierce, R. A., Mollah, S., Shabanowitz, J., Eisenlohr, L. C., van Veelen, P., Ossendorp, F., Hunt, D. F., Goulmy, E. and Engelhard, V. H.
TITLE	The minor histocompatibility antigen HA-3 arises from differential proteasome-mediated cleavage of the lymphoid blast crisis (Lbc) oncoprotein
JOURNAL	Blood 102 (2), 621–629 (2003)
MEDLINE	22718699
PUBMED	12663445
REMARK	GeneRIF: The HA-3 peptide, VTEPGTAQY, is encoded by the lymphoid blast crisis oncogene, showing for the 1st time that a leukemia-associated oncogene can give rise to immunogenic T-cell epitopes that may participate in antihost & antileukemic alloimmune responses.
REFERENCE	2 (residues 1 to 2817)
AUTHORS	Park, B., Nguyen, N. T., Dutt, P., Merdek, K. D., Bashar, M., Sterpetti, P., Tosolini, A., Testa, J. R. and Toksoz, D.
TITLE	Association of Lbc Rho guanine nucleotide exchange factor with alpha-catenin-related protein, alpha-catulin/CTNNAL1, supports serum response factor activation
JOURNAL	J. Biol. Chem. 277 (47), 45361–45370 (2002)
MEDLINE	22323310
PUBMED	12270917
REMARK	GeneRIF: Results show that alpha-catulin co-expression leads to increased Lbc-induced serum response factor activation and may modulate Rho pathway signaling in vivo by providing a scaffold for the Lbc Rho guanine nucleotide exchange factor.
REFERENCE	3 (residues 1 to 2817)
AUTHORS	Diviani, D., Soderling, J. and Scott, J. D.
TITLE	AKAP-Lbc anchors protein kinase A and nucleates Galpha 12-selective Rho-mediated stress fiber formation
JOURNAL	J. Biol. Chem. 276 (47), 44247–44257 (2001)
MEDLINE	21570178
PUBMED	11546812
REFERENCE	4 (residues 1 to 2817)
AUTHORS	Klussmann, E., Edemir, B., Pepperle, B., Tamma, G., Henn, V., Klauschenz, E., Hundsrucker, C., Maric, K. and Rosenthal, W.
TITLE	Ht31: the first protein kinase A anchoring protein to integrate protein kinase A and Rho signaling
JOURNAL	FEBS Lett. 507 (3), 264–268 (2001)
MEDLINE	21553155
PUBMED	11696353
REFERENCE	5 (residues 1 to 2817)
AUTHORS	Sterpetti, P., Hack, A. A., Bashar, M. P., Park, B., Cheng, S. D., Knoll, J. H., Urano, T., Feig, L. A. and Toksoz, D.
TITLE	Activation of the Lbc Rho exchange factor proto-oncogene by truncation of an extended C terminus that regulates transformation and targeting
JOURNAL	Mol. Cell. Biol. 19 (2), 1334–1345 (1999)
MEDLINE	99108106
PUBMED	9891067
REFERENCE	6 (residues 1 to 2817)
AUTHORS	Rubino, D., Driggers, P., Arbit, D., Kemp, L., Miller, B., Coso, O., Pagliai, K., Gray, K., Gutkind, S. and Segars, J.

-continued

NP_006729. A kinase anchor protein 13 isoform 1 [gi: 31563330]

TITLE	Characterization of Brx, a novel Dbl family member that modulates estrogen receptor action
JOURNAL	Oncogene 16 (19), 2513–2526 (1998)
MEDLINE	98288806
PUBMED	9627117
REFERENCE	7 (residues 1 to 2817)
AUTHORS	Toksoz, D. and Williams, D. A.
TITLE	Novel human oncogene lbc detected by transfection with distinct homology regions to signal transduction products
JOURNAL	Oncogene 9 (2), 621–628 (1994)
MEDLINE	94119604
PUBMED	8290273
REFERENCE	8 (residues 1 to 2817)
AUTHORS	Carr, D. W., Hausken, Z. E., Fraser, I. D., Stofko-Hahn, R. E. and Scott, J. D.
TITLE	Association of the type II cAMP-dependent protein kinase with a human thyroid RII-anchoring protein. Cloning and characterization of the RII-binding domain
JOURNAL	J. Biol. Chem. 267 (19), 13376–13382 (1992)
MEDLINE	92317056
PUBMED	1618839
REFERENCE	9 (residues 1 to 2817)
AUTHORS	Carr, D. W., Stofko-Hahn, R. E., Fraser, I. D., Bishop, S. M., Acott, T. S., Brennan, R. G. and Scott, J. D.
TITLE	Interaction of the regulatory subunit (RII) of cAMP-dependent protein kinase with RII-anchoring proteins occurs through an amphipathic helix binding motif
JOURNAL	J. Biol. Chem. 266 (22), 14188–14192 (1991)
MEDLINE	91317762
PUBMED	1860836
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AF406992.1, AB055890.1, AK091210.1, AL135297.1 and BC050312.1. On Jun 10, 2003 this sequence version replaced gi: 21493026. Summary: The A-kinase anchor proteins (AKAPs) are a group of structurally diverse proteins, which have the common function of binding to the regulatory subunit of protein kinase A (PKA) and confining the holoenzyme to discrete locations within the cell. This gene encodes a member of the AKAP family. Alternative splicing of this gene results in at least 3 transcript variants encoding different isoforms containing a dbl oncogene homology (DH) domain and a pleckstrin homology (PH) domain. The DH domain is associated with guanine nucleotide exchange activation for the Rho/Rac family of small GTP binding proteins, resulting in the conversion of the inactive GTPase to the active form capable of transducing signals. The PH domain has multiple functions. Therefore, these isoforms function as scaffolding proteins to coordinate a Rho signaling pathway and, in addition, function as protein kinase A-anchoring proteins. Transcript Variant: This variant (1) encodes the longest isoform (1).
FEATURES	Location/Qualifiers
source	1 . . . 2817 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="15" /map="15q24–q25"
Protein	1 . . . 2817 /product="A-kinase anchor protein 13 isoform 1" /note="A-kinase anchoring protein; guanine nucleotide exchange factor Lbc; breast cancer nuclear receptor-binding auxiliary protein; lymphoid blast crisis oncogene"
Region	166 . . . 224 /region_name="ankyrin repeats"
variation	452 /allele="T" /allele="M" /db_xref="dbSNP:2061821"
variation	494 /allele="W" /allele="R" /db_xref="dbSNP:2061822"

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NP_006729. A kinase anchor protein 13 isoform 1 [gi: 31563330]	
variation	574 /allele="R" /allele="C" /db_xref="dbSNP:2061824"
variation	624 /allele="V" /allele="G" /db_xref="dbSNP:745191"
variation	689 /allele="K" /allele="E" /db_xref="dbSNP:7177107"
variation	845 /allele="V" /allele="A" /db_xref="dbSNP:4075256"
variation	897 /allele="V" /allele="M" /db_xref="dbSNP:4075254"
variation	1062 /allele="P" /allele="A" /db_xref="dbSNP:4843074"
variation	1086 /allele="N" /allele="D" /db_xref="dbSNP:4843075"
variation	1216 /allele="T" /allele="M" /db_xref="dbSNP:7162168"
Region	1792 . . . 1830 /region name="C1 homology region"
Region	2002 . . . 2193 /region_name="Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases" /note="RhoGEF" /db_xref="CDD:smart00325"
variation	2183 /allele="N" /allele="S" /db_xref="dbSNP:3743323"
variation	2461 /allele="G" /allele="S" /db_xref="dbSNP:2241268"
variation	2805 /allele="A" /allele="T" /db_xref="dbSNP:2614668"
CDS	1 . . . 2817 /gene="AKAP13" /coded_by="NM_006738.4:171..8624" /note="go_component: membrane fraction [goid 0005624] [evidence E]; go_function: protein kinase A anchoring activity [goid 0005079] [evidence E] [pmid 1618839]; go_function: protein binding [goid 0005515] [evidence E] [pmid 1860836]; go function: Rho guanyl-nucleotide exchange factor activity [goid 0005089] [evidence NR]; go_function: signal transducer activity [goid 0004871] [evidence P]; go_process: oncogenesis [goid 0007048] [evidence P]; go_process: signal transduction [goid 0007165] [evidence NR]" /db_xref="GeneID:11214" /db_xref="LocusID:11214" /db_xref="MIM:604686"

[0063] Origin

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   1 mklnpqqapl ygdcvvtvll aeedkaeddv vfylvflgst  lrhctstrkv ssdtletiap [SEQ ID NO:17]
  61 ghdccetvkv qlcaskegip vfvvaeedfh fvqdeaydaa qflatsagnq  qalnftrfld
 121 qsgppsgdvn sldkklvlaf rhlklptewn vlgtdqslhd agpretlmhf avrlgllrlt
 181 wfllqkpggr  galsihnqeg atpvslaler gyhklhqllt eenagepdsw sslsyeipyg
 241 dcsvrhhrel diytltsesd shhehpfpgd gctgpifklm niqqqlmktn lkqmdslmpl
 301 mmtaqdpssa petdgqflpc  apeptdpqrl ssseetestq ccpgspvaqt espcdlssiv
 361 eeentdrscr kknkgverkg eevepapivd sgtvsdqdsc lqslpdcgvk gteglsscgn
 421 rneetgtkss gmptdqesls sgdavlqrdl vmepgtaqys sggelggist tnvstpdtag
 481 emehglmnpd atvwknvlqg gestkerfen snigtagasd vhvtskpvdk isvpncapaa
 541 ssldgnkpae sslafsneet stektaetet srsreesada pvdqnsvvip aaakdkisdg
 601 lepytllaag igeamspsdl allgleedvm phqnsetnss haqsqkgkss picsttgddk
 661 lcadsacqqn tvtssgdlva klcdnivses esttarqpss qdppdashce dpqahtvtsd
 721 pvrdtqerad fcpfkvvdnk gqrkdvkldk pltnmlevvs hphpvvpkme kelvpdqavi
 781 sdstfslans pgsesvtkdd alsfvpsqke kgtatpelht atdyrdgpdg nsnepdtrpl
 841 edravglsts staaelqhgm gntsltglgg ehegpappai pealnikgnt dsslqsvgka
 901 tlaldsvlte egkllvvses saaqeqdkdk avtcssiken alssgtlqee qrtpppgqdt
 961 qqfheksisa dcakdkalql snspgassaf lkaetehnke vapqvslltq ggaaqslvpp
1021 gaslatesrq ealgaehnss allpcllpdg sdgsdalncs qpspldvgvk ntqsqgktsa
1081 cevsgdvtvd vtgvnalqgm aeprrenish ntqdilipnv llsqeknavl glpvalqdka
1141 vtdpqgvgtp emipldwekg klegadhsct mgdaeeaqid deahpvllqp vakelptdme
1201 lsahddgapa gvrevmrapp sgrerstpsl pcmvsaqdap lpkgadliee aasrivdavi
1261 eqvkaagall tegeachmsl sspelgpltk glesaftekv stfppgeslp mgstpeeatg
1321 slagcfagre epekiilpvq gpepaaempd vkaedevdfr assiseevav gsiaatlkmk
1381 qgpmtqainr enwctiepcp daasllaskq specenfldv  glgrectskq gvlkresgsd
1441 sdlfhspsdd mdsiifpkpe eehlacditg sssstddtas ldrhsshgsd vslsqilkpn
1501 rsrdrqsldg fyshgmgaeg resesepadp gdveeeemds itevpancsv lrssmrslsp
1561 frrhswgpgk naasdaemnh rsmswcpsgv qysaglsadf nyrsfslegl tggagvgnkp
1621 ssslevssan aeelrhpfsg eervdslvsl seedlesdqr ehrmfdqqic hrskqqgfny
1681 ctsaissplt ksislmtish pgldnsrpfh stfhntsanl tesiteenyn flphspskkd
1741 sewksgtkvs rtfsyiknkm ssskkskeke kekdkikeke kdskdkekdk ktvnghtfss
1801 ipvvgpiscs qcmkpftnkd aytcancsaf vhkgcresla scakvkmkqp kgslqahdts
1861 slptvimrnk psqpkerprs avllvdetat tpifanrrsq qsvslsksvs iqnitgvgnd
1921 enmsntwkfl  shstdslnki skvnestesl tdegvgtdmn egqllgdfei eskqleaesw
1981 sriidskflk  qqkkdvvkrq eviyelmqte fhhvrtlkim sgvysqgmma dllfeqqmve
2041 klfpcldeli sihsqffqri lerkkeslvd kseknflikr  igdvlvnqfs genaerlkkt
2101 ygkfcgqhnq svnyfkdlya kdkrfqafvk kkmsssvvrr lgipecillv tqritkypvl
2161 fqrilqctkd neveqedlaq slslvkdvig avdskvasye kkvrlneiyt ktdsksimrm
2221 ksgqmfaked lkrkklvrdg svflknaagr  lkevqavllt dilvflqekd  qkyifasldq
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2281 kstvislkkl  ivrevaheek  glflismgmt   dpemvevhas  skeernswiq  iiqdtintln

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2401 cspthsprvl  frsnteealk  ggplmksain  eveilqglvs  gnlggtlgpt  vsspieqdvv

2461 gpvslprrae  tfggfdshqm  naskggekee  gddgqdlrrt  esdsglkkgg  nanlvfmlkr

2521 nseqvvqsvv  hlyellsalq  gvvlqqdsyi  edqklvlser  altrslsrps  slieqekqrs

2581 lekqrqdlan  lqkqqaqyle  ekrrrerewe  arerelrere  allaqreeev  qqgqqdleke

2641 reelqqkkgt  yqydlerlra  aqkqlereqe  qlrreaerls  qrqterdlcq  vshphtklmr

2701 ipsffpspee  ppspsapsia  ksgsldsels  vspkrnsisr  thkdkgpfhi  lsstsqtnkg

2761 pegqsqapas  tsastrlfgl  tkpkekkekk  kknktsrsqp  gdgpasevsa  egeeifc
```

[0064]

NP_658913. A-kinase anchor protein 13 isoform 3 [gi: 21493031]

LOCUS	NP_658913 1058 aa linear PRI 05-OCT-2003
DEFINITION	A-kinase anchor protein 13 isoform 3; A-kinase anchoring protein; guanine nucleotide exchange factor Lbc; breast cancer nuclear receptor-binding auxiliary protein; lymphoid blast crisis oncogene [*Homo sapiens*].
ACCESSION	NP_658913
VERSION	NP_658913.1 GI: 21493031
DBSOURCE	REFSEQ: accession NM 144767.3
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 1058)
AUTHORS	Spierings, E., Brickner, A. G., Caldwell, J. A., Zegveld, S., Tatsis, N., Blokland, E., Pool, J., Pierce, R. A., Mollah. S., Shabanowitz, J., Eisenlohr, L. C., van Veelen, P., Ossendorp, F., Hunt, D. F., Goulmy, E. and Engelhard, V. H.
TITLE	The minor histocompatibility antigen HA-3 arises from differential proteasome-mediated cleavage of the lymphoid blast crisis (Lbc) oncoprotein
JOURNAL	Blood 102 (2), 621–629 (2003)
MEDLINE	22718699
PUBMED	12663445
REMARK	GeneRIF: The HA-3 peptide, VTEPGTAQY, is encoded by the lymphoid blast crisis oncogene, showing for the 1st time that a leukemia-associated oncogene can give rise to immunogenic T-cell epitopes that may participate in antihost & antileukemic alloimmune responses.
REFERENCE	2 (residues 1 to 1058)
AUTHORS	Park, B., Nguyen, N. T., Dutt, P., Merdek, K. D., Bashar, M., Sterpetti, P., Tosolini, A., Testa, J. R. and Toksoz, D.
TITLE	Association of Lbc Rho guanine nucleotide exchange factor with alpha-catenin-related protein, alpha-catulin/CTNNAL1, supports serum response factor activation
JOURNAL	J. Biol. Chem. 277 (47), 45361–45370 (2002)
MEDLINE	22323310
PUBMED	12270917
REMARK	GeneRIF: Results show that alpha-catulin co-expression leads to increased Lbc-induced serum response factor activation and may modulate Rho pathway signaling in vivo by providing a scaffold for the Lbc Rho guanine nucleotide exchange factor.
REFERENCE	3 (residues 1 to 1058)
AUTHORS	Diviani, D., Soderling, J. and Scott, J. D.
TITLE	AKAP-Lbc anchors protein kinase A and nucleates Galpha 12-selective Rho-mediated stress fiber formation
JOURNAL	J. Biol. Chem. 276 (47), 44247–44257 (2001)
MEDLINE	21570178
PUBMED	11546812

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NP_658913. A-kinase anchor protein 13 isoform 3 [gi: 21493031]

REFERENCE	4 (residues 1 to 1058)
AUTHORS	Klussmann, E., Edemir, B., Pepperle, B., Tamma, G., Henn, V., Klauschenz, E., Hundsrucker, C., Maric, K. and Rosenthal, W.
TITLE	Ht31: the first protein kinase A anchoring protein to integrate protein kinase A and Rho signaling
JOURNAL	FEBS Lett. 507 (3), 264–268 (2001)
MEDLINE	21553155
PUBMED	11696353
REFERENCE	5 (residues 1 to 1058)
AUTHORS	Sterpetti, P., Hack, A. A., Bashar, M. P., Park, B., Cheng, S. D., Knoll, J. H., Urano, T., Feig, L. A. and Toksoz, D.
TITLE	Activation of the Lbc Rho exchange factor proto-oncogene by truncation of an extended C terminus that regulates transformation and targeting
JOURNAL	Mol. Cell. Biol. 19 (2), 1334–1345 (1999)
MEDLINE	99108106
PUBMED	9891067
REFERENCE	6 (residues 1 to 1058)
AUTHORS	Rubino, D., Driggers, P., Arbit, D., Kemp, L., Miller, B., Coso, O., Pagliai, K., Gray, K., Gutkind, S. and Segars, J.
TITLE	Characterization of Brx, a novel Dbl family member that modulates estrogen receptor action
JOURNAL	Oncogene 16 (19), 2513–2526 (1998)
MEDLINE	98288806
PUBMED	9627117
REFERENCE	7 (residues 1 to 1058)
AUTHORS	Toksoz, D. and Williams, D. A.
TITLE	Novel human oncogene lbc detected by transfection with distinct homology regions to signal transduction products
JOURNAL	Oncogene 9 (2), 621–628 (1994)
MEDLINE	94119604
PUBMED	8290273
REFERENCE	8 (residues 1 to 1058)
AUTHORS	Carr, D. W., Hausken, Z. E., Fraser, I. D., Stofko-Hahn, R. E. and Scott, J. D.
TITLE	Association of the type II cAMP-dependent protein kinase with a human thyroid RII-anchoring protein. Cloning and characterization of the RII-binding domain
JOURNAL	J. Biol. Chem. 267 (19), 13376–13382 (1992)
MEDLINE	92317056
PUBMED	1618839
REFERENCE	9 (residues 1 to 1058)
AUTHORS	Carr, D. W., Stofko-Hahn, R. E., Fraser, I. D., Bishop, S. M., Acott, T. S., Brennan, R. G. and Scott, J. D.
TITLE	Interaction of the regulatory subunit (RII) of cAMP-dependent protein kinase with RII-anchoring proteins occurs through an amphipathic helix binding motif
JOURNAL	J. Biol. Chem. 266 (22), 14188–14192 (1991)
MEDLINE	91317762
PUBMED	1860836
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AF127481.1, AB055890.1, AK091210.1 and AL135297.1. Summary: The A-kinase anchor proteins (AKAPs) are a group of structurally diverse proteins, which have the common function of binding to the regulatory subunit of protein kinase A (PKA) and confining the holoenzyme to discrete locations within the cell. This gene encodes a member of the AKAP family. Alternative splicing of this gene results in at least 3 transcript variants encoding different isoforms containing a dbl oncogene homology (DH) domain and a pleckstrin homology (PH) domain. The DH domain is associated with guanine nucleotide exchange activation for the Rho/Rac family of small GTP binding proteins, resulting in the conversion of the inactive GTPase to the active form capable of transducing signals. The PH domain has multiple functions. Therefore, these isoforms function as scaffolding proteins to coordinate a Rho signaling pathway and, in addition, function as protein kinase A-anchoring proteins. Transcript Variant: This variant (3) lacks most of the 5' exons and has an alternate 5' exon, as compared to variant 1. It uses a downstream in-frame start codon, and the resulting isoform 3 is shorter but has an identical C-terminus, compared to isoform 1. Sequence Note: The sequence AF127481.1 is a chimeric mRNA clone. Only the AKAP13 region was propagated into this RefSeq record.

-continued

NP_658913. A-kinase anchor protein 13 isoform 3 [gi: 21493031]

FEATURES	Location/Qualifiers
source	1 . . . 1058 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="15" /map="15q24–q25"
Protein	1 . . . 1058 /product="A-kinase anchor protein 13 isoform 3" /note="A-kinase anchoring protein; guanine nucleotide exchange factor Lbc; breast cancer nuclear receptor-binding auxiliary protein; lymphoid blast crisis oncogene"
Region	33 . . . 71 /region_name="C1 homology region"
Region	243 . . . 434 /region name="Guanine nucleotide exchange factor for Rho/Rac/Cdc42-like GTPases" /note="RhoGEF" /db_xref="CDD:smart00325"
variation	424 /allele="N" /allele="S" /db_xref="dbSNP:3743323"
variation	702 /allele="G" /allele="S" /db_xref="dbSNP:2241268"
variation	1046 /allele="A" /allele="T" /db_xref="dbSNP:2614668"
CDS	1 . . . 1058 /gene="AKAP13" /coded_by="NM_144767.3:227..3403" /note="go component: membrane fraction [goid 0005624] [evidence E]; go function: protein kinase A anchoring activity [goid 0005079] [evidence E] [pmid 1618839]; go function: protein binding [goid 0005515] [evidence E] [pmid 1860836]; go function: Rho guanyl-nucleotide exchange factor activity [goid 0005089] [evidence NR]; go function: signal transducer activity [goid 0004871] [evidence P]; go_process: oncogenesis [goid 0007048] [evidence P]; go_process: signal transduction [goid 0007165] [evidence NR]" /db_xref="GeneID:11214" /db_xref="LocusID:11214" /db_xref="MIM:604686"

[**0065**] Origin

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  61 daytcancsa  fvhkgcresl  ascakvkmkq  pkgslqahdt  sslptvimrn  kpsqpkerpr

 121 savllvdeta  ttpifanrrs  qqsvslsksv  siqnitgvgn  denmsntwkf  lshstdslnk

 181 iskvnestes  ltdegvgtdm  negqllgdfe  ieskqleaes  wsriidskfl   kqqkkdvvkr

 241 qeviyelmqt  efhhvrtlki  msgvysqgmm  adllfeqqmv  eklfpcldel  isihsqffqr

 301 ilerkkeslv  dkseknflik   rigdvlvnqf  sgenaerlkk  tygkfcgqhn  qsvnyfkdly

 361 akdkrfqafv  kkkmsssvvr  rlgipecill  vtqritkypv  lfqrilqctk  dneveqedla

 421 qslslvkdvi  gavdskvasy  ekkvrlneiy  tktdsksimr  mksgqmfake  dlkrkklvrd
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 481 gsvflknaag  rlkevqavll  tdilvflqek  dqkyifasld  qkstvislkk  livrevahee

 541 kglflismgm  tdpemvevha  sskeernswi  qiiqdtintl  nrdedegips  eneeekkmld

 601 trarelkeql  hqkdqkilll  leekemifrd  maecstplpe  dcspthsprv  lfrsnteeal

 661 kggplmksai  neveilqglv  sgnlggtlgp  tvsspieqdv  vgpvslprra  etfggfdshq

 721 mnaskggeke  egddgqdlrr  tesdsglkkg  gnanlvfmlk  rnseqvvqsv  vhlyellsal

 781 qgvvlqqdsy  iedqklvlse  raltrslsrp  sslieqekqr  slekgrqdla  nlqkqqaqyl

 841 eekrrrerew  earerelrer  eallaqreee  vqqgqqdlek  ereelqqkkg  tyqydlerlr

 901 aaqkqlereq  eqlrreaerl  sqrqterdlc  qvshphtklm  ripsffpspe  eppspsapsi

 961 aksgsldsel  svspkrnsis  rthkdkgpfh  ilsstsqtnk  gpeggsqapa  stsastrlfg

1021 ltkpkekkek  kkknktsrsq  pgdgpasevs  aegeeifc
```

[0066] IJ. ATP Citrate Lyase

[0067] ATP citrate lyase has been identified as an Akt substrate that interacts with Akt. ATP citrate lyase is associated with reference sequence NP_001087 (GenBank Accession No. 4501865). Other relevant sequences include rat citrate lyase associated with reference sequence NP_058683 (GenBank Accession No. 8392839).

NP_001087. ATP citrate lyase [gi: 4501865]

LOCUS	NP_001087 1105 aa linear PRI 04-OCT-2003
DEFINITION	ATP citrate lyase [*Homo sapiens*].
ACCESSION	NP_001087
VERSION	NP_001087.1 GI: 4501865
DBSOURCE	REFSEQ: accession NM 001096.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE	1 (residues 1 to 1105)
AUTHORS	Couch, F. J., Abel, K. J., Brody, L. C., Boehnke, M., Collins, F. S. and Weber, B. L.
TITLE	Localization of the gene for ATP citrate lyase (ACLY) distal to gastrin(GAS) and proximal to D17S856 on chromosome 17q12–q21
JOURNAL	Genomics 21 (2), 444–446 (1994)
MEDLINE	94375075
PUBMED	8088842
REFERENCE	2 (residues 1 to 1105)
AUTHORS	Elshourbagy, N. A., Near, J. C., Kmetz, P. J., Wells, T. N., Groot, P. H., Saxty, B. A., Hughes, S. A., Franklin, M. and Gloger, I. S.
TITLE	Cloning and expression of a human ATP-citrate lyase cDNA
JOURNAL	Eur. J. Biochem. 204 (2), 491–499 (1992)
MEDLINE	92174902
PUBMED	1371749
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from X64330.1. Summary: ATP citrate lyase is the primary enzyme responsible for the synthesis of cytosolic acetyl-CoA in many tissues. The enzyme is a tetramer (relative molecular weight approximately 440,000) of apparently identical subunits. It catalyzes the formation of acetyl-CoA and oxaloacetate from citrate and CoA with a concomitant hydrolysis of ATP to ADP and phosphate. The product, acetyl-CoA, serves several important biosynthetic pathways, including lipogenesis and cholesterogenesis. In nervous tissue, ATP citrate-lyase may be involved in the biosynthesis of acetylcholine.
FEATURES	Location/Qualifiers
source	1. . . 1105 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="17" /map="17q12–q21"

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NP_001087. ATP citrate lyase [gi: 4501865]	
Protein	1 . . . 1105 /product="ATP citrate lyase" /EC_number="4.1.3.8"
Region	6 . . . 415 /region name="Succinyl-CoA synthetase, beta subunit [Energy production and conversion]" /note="SucC" /db_xref="CDD:COG0045"
Region	554 . . . 809 /region_name="Succinyl-CoA synthetase, alpha subunit [Energy production and conversion]" /note="SucD" /db_xref="CDD:COG0074"
CDS	1 . . . 1105 /gene="ACLY" /coded_by="NM_001096.1:85..3402" /note="go_component: citrate lyase complex [goid 0009346] [evidence TAS] [pmid 1371749]; go_function: ATP citrate synthase activity [goid 0003878] [evidence TAS] [pmid 1371749]; go function: transferase activity [goid 0016740] [evidence IEA]; go_function: ATP citrate synthase activity [goid 0046913] [evidence IEA]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_function: magnesium ion binding [goid 0000287] [evidence IEA]; go_function: lyase activity [goid 0016829] [evidence IEA]; go_function: citrate (Si)-synthase activity [goid 0004108] [evidence IEA]; go_process: ATP catabolism [goid 0006200] [evidence TAS] [pmid 1371749]; go_process: coenzyme A metabolism [goid 0015936] [evidence TAS] [pmid 1371749]; go_process: citrate metabolism [goid 0006101] [evidence TAS] [pmid 1371749]; go_process: metabolism [goid 0008152] [evidence IEA]; go_process: lipid biosynthesis [goid 0008610] [evidence IEA]; go_process: tricarboxylic acid cycle [goid 0006099] [evidence IEA]" /db_xref="GeneID:47" /db_xref="LocusID:47" /db_xref="MIM:108728"

[**0068**] Origin

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   1 msakaiseqt  gkellykfic   ttsaiqnrfk  yarvtpdtdw  arllqdhpwl  lsqnlvvkpd  [SEQ ID NO:19]
  61 qlikrrgklg  lvgvdltldg  vkswlkprlg  qeatvgkatg  flknfliepf    aphsqaeefy
 121 vciyatregd  yvlfhheggv  dvgdvdakaq  kllvgvdekl  npedikkhll  vhapddkkei
 181 lasfisglfn   fyedlyftyl  einplvvtkd  gvyvldlaak  vdatadyick  vkwgdiefpp
 241 pfgrvaypee  ayiadldaks  gaslkltlln  pkgriwtmva  gggasvvysd  ticdlggvne
 301 lanygeysga  pseqqtydya  ktilslmtre  khpdgkilii  ggsianftnv  aatfkgivra
 361 irdyqgplke  hevtifvrrg  gpnyqeglrv  mgevgkttgi  pihvfgteth  mtaivgmawa
 421 paipnqppta  ahtanfllna   qretstpaps  rtasfyesmv  devradevap  akkakpampq
 481 dsvpsprslq  gksttlfsrh  tkaivwgmqt  ravqgmldfd  yvcsrdepsv  aamvypftgd
 541 hkqkfywghk  eilipvfknm  adamrkhpev  dvlinfaslr  saydstmetm  nyaqirtiai
 601 iaegipealt  rklikkadqk  gvtiigpatv  ggikpgcfki  gntggmldni  lasklypqaa
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 661 vayvsrsggm  snelnniisr  ttdgvyegva  iggdrypgst  fmdhvlryqd  tpgvkmivvl

 721 geiggteeyk  isrgikegrl  tkpivcwcig  tcatmfssev  qfghagacan  qasetavakn

 781 qalkeagvfv  prsfdelgei  iqsvyedlva  ngvivpaqev  ppptvpmdys  warelglirk

 841 pasfmtsicd  ergqeliyag  mpitevfkee  mgiggalgll  wfqkrlpkys  cqfiemclmv

 901 tadhgpavsg  ahntiicart  avelvsslts  glltigdrfg  galdaaakmf  skafdsgiip

 961 mefvnkmkke  gklimgighr  vksinnpdmr  vqilkdyvrq  hfpatplldy  alevekitts

1021 kkpnlilnvd  gligvafvdm  lrncgsftre  eadeyidiga  lngifvlgrs  mgfighyldq

1081 krlkqglyrh  pwddisyvlp  ehmsm
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[**0069**] IK Chromodomain Helicase DNA Binding Protein 4 (Mi-2b)

[**0070**] Chromodomain helicase DNA binding protein 4 (Mi-2b) has been identified as an Akt substrate that interacts with Akt. Mi-2b is associated with reference sequence NP_001264 (GenBank Accession No. 4557453).

NP_001264. chromodomain helicase DNA binding protein 4; Mi-2b [gi: 4557453]

LOCUS	NP_001264 1912 aa linear PRI 04-OCT-2003
DEFINITION	chromodomain helicase DNA binding protein 4; Mi-2b [*Homo sapiens*].
ACCESSION	NP_001264
VERSION	NP_001264.1 GI: 4557453
DBSOURCE	REFSEQ: accession NM 001273.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 1912)
AUTHORS	Zhang, Y., LeRoy, G., Seelig, H. P., Lane, W. S. and Reinberg, D.
TITLE	The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities
JOURNAL	Cell 95 (2), 279–289 (1998)
MEDLINE	99005195
PUBMED	9790534
REFERENCE	2 (residues 1 to 1912)
AUTHORS	Woodage, T., Basrai, M. A., Baxevanis, A. D., Hieter, P. and Collins, F. S.
TITLE	Characterization of the CHD family of proteins
JOURNAL	Proc. Natl. Acad. Sci. U.S.A. 94 (21), 11472–11477 (1997)
MEDLINE	97470991
PUBMED	9326634
REFERENCE	3 (residues 1 to 1912)
AUTHORS	Seelig, H. P., Renz, M., Targoff, I. N., Ge, Q. and Frank, M. B.
TITLE	Two forms of the major antigenic protein of the dermatomyositis-specific Mi-2 autoantigen
JOURNAL	Arthritis Rheum. 39 (10), 1769–1771 (1996)
MEDLINE	97000821
PUBMED	8843877
REFERENCE	4 (residues 1 to 1912)
AUTHORS	Seelig, H. P., Moosbrugger, I., Ehrfeld, H., Fink, T., Renz, M. and Genth, E.
TITLE	The major dermatomyositis-specific Mi-2 autoantigen is a presumed helicase involved in transcriptional activation
JOURNAL	Arthritis Rheum. 38 (10), 1389–1399 (1995)
MEDLINE	96017437
PUBMED	7575689
REFERENCE	5 (residues 1 to 1912)
AUTHORS	Ge, Q., Nilasena, D. S., O'Brien, C. A., Frank, M. B. and Targoff, I. N.
TITLE	Molecular analysis of a major antigenic region of the 240-kD protein of Mi-2 autoantigen

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NP_001264. chromodomain helicase DNA binding protein 4; Mi-2b [gi: 4557453]

JOURNAL	J. Clin. Invest. 96 (4), 1730–1737 (1995)
MEDLINE	96013633
PUBMED	7560064
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from X86691.1. Summary: The CHD family of proteins is characterized by the presence of chromo (chromatin organization modifier) domains and SNF2-related helicase/ATPase domains. Patients with dermatomyositis develop antibodies against the nuclear antigen chromodomain helicase DNA binding protein 4. The protein exists in a complex containing histone deacetylase and nucleosome remodeling activities, suggesting a role for chromatin reorganization in cancer metastasis.
FEATURES	Location/Qualifiers
source	1 . . . 1912 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="12" /map="12p13"
Protein	1 . . . 1912 /product="chromodomain helicase DNA binding protein 4" /note="Mi-2b"
variation	139 /allele="D" /allele="E" /db_xref="dbSNP:1639122"
Region	372 . . . 417 /region_name="PHD-finger. PHD folds into an interleaved type of Zn-finger chelating 2 Zn ions in a similar manner to that of the RING and FYVE domains" /note="PHD" /db_xref="CDD:pfam00628"
Region	451 . . . 496 /region_name="PHD-finger. PHD folds into an interleaved type of Zn-finger chelating 2 Zn ions in a similar manner to that of the RING and FYVE domains" /note="PHD" /db_xref="CDD:pfam00628"
Region	540 . . . 579 /region name="Chromatin organization modifier domain" /note="CHROMO" /db_xref="CDD:smart00298"
Region	622 . . . 676 /region name="Chromatin organization modifier domain" /note="CHROMO" /db_xref="CDD:smart00298"
Region	708 . . . 1222 /region_name="Superfamily II DNA/RNA helicases, SNF2 family [Transcription/DNA replication, recombination, and repair]" /note="HepA" /db_xref="CDD:COG0553"
CDS	1 . . . 1912 /gene="CHD4" /coded_by="NM_001273.1:90..5828" /note="go component: chromatin [goid 0005717] [evidence IEA]; go_component: nucleus [goid 0005634] [evidence IEA]; go_function: ATP dependent DNA helicase activity [goid 0004003] [evidence TAS] [pmid 9326634]; go function: zinc ion binding [goid 0008270] [evidence TAS] [pmid 7560064]; go function: DNA binding [goid 0003677] [evidence P] [pmid 9326634]; go function: chromatin binding [goid 0003682] [evidence IEA]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_process: chromosome organization and biogenesis (sensu Eukarya) [goid 0007001] [evidence TAS] [pmid 9326634]; go_process: regulation of transcription from Pol II promoter [goid 0006357] [evidence TAS] [pmid 9326634]; go_process: chromatin assembly/disassembly [goid 0006333] [evidence IEA];

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NP_001264. chromodomain helicase DNA binding protein 4; Mi-2b [gi: 4557453]
go_process: chromatin modification [goid 0016568] [evidence IEA]" /db_xref="GeneID:1108" /db_xref="LocusID:1108" /db_xref="MIM:603277"

[0071] Origin

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   1 masglgspsp  csagseeedm  dallnnslpp  phpeneedpe  edlsetetpk  lkkkkkpkkp  [SEQ ID NO:20]
  61 rdpkipkskr  qkkermllcr  qlgdssgegp  efveeeeeva  lrsdsegsdy  tpgkkkkkkl
 121 gpkkekksks  krkeeeeedd  ddddskepks  saqlledwgm  edidhvfsee  dyrtltnyka
 181 fsqfvrplia  aknpkiavsk  mmmvlgakwr  efstnnpfkg  ssgasvaaaa  aaavavvesm
 241 vtatevappp  ppvevpirka  ktkegkgpna  rrkpkgsprv  pdakkpkpkk  vaplkiklgg
 301 fgskrkrsss  edddldvesd  fddasinsys  vsdgstsrss  rsrkklrttk  kkkkgeeevt
 361 avdgyetdhq  dycevcqqgg  eiilcdtcpr  ayhmvcldpd  mekapegkws  cphcekegiq
 421 weakednseg  eeileevggd  leeeddhhme  fcrvckdgge  llccdtcpss  yhihclnppl
 481 peipngewlc  prctcpalkg  kvqkiliwkw  gqppsptpvp  rppdadpntp  spkplegrpe
 541 rqffvkwqgm  sywhcswvse  lqlelhcqvm  frnyqrkndm  deppsgdfgg  deeksrkrkn
 601 kdpkfaemee  rfyrygikpe  wmmihrilnh  svdkkghvhy  likwrdlpyd  qaswesedve
 661 iqdydlfkqs  ywnhrelmrg  eegrpgkklk  kvklrklerp  petptvdptv  kyerqpeyld
 721 atggtlhpyq  meglnwlrfs  waqgtdtila  demglgktvq  tavflyslyk  eghskgpflv
 781 saplstiinw  erefemwapd  myvvtyvgdk  dsraiirene  fsfednairg  gkkasrmkke
 841 asvkfhvllt  syelitidma  ilgsidwacl  ivdeahrlkn  nqskffrvln  gyslqhklll
 901 tgtplqnnle  elfhllnflt  perfhnlegf  leefadiake  dqikklhdml  gphmlrrlka
 961 dvfknmpskt  elivrvelsp  mqkkyykyil  trnfealnar  gggnqvslln  vvmdlkkccn
1021 hpylfpvaam  eapkmpngmy  dgsalirasg  kllllqkmlk  nlkegghrvl  ifsqmtkmld
1081 lledfleheg  ykyeridggi  tgnmrqeaid  rfnapgaqqf  cfllstragg  lginlatadt
1141 viiydsdwnp  hndiqafsra  hrigqnkkvm  iyrfvtrasv  eeritqvakk  kmmlthlvvr
1201 pglgsktgsm  skqelddilk  fgteelfkde  atdgggdnke  gedssvihyd  dkaierlldr
1261 nqdetedtel  qgmneylssf  kvaqyvvree  emgeeeever  eiikqeesvd  pdywekllrh
1321 hyeqqqedla  rnlgkgkrir  kqvnyndgsq  edrdwqddqs  dnqsdysvas  eegdedfder
1381 seaprrpsrk  glrndkdkpl  ppllarvggn  ievlgfnarq  rkaflnaimr  ygmppqdaft
1441 tqwlvrdlrg  ksekefkayv  slfmrhlcep  gadgaetfad  gvpreglsrq  hvltrigvms
1501 lirkkvqefe  hvngrwsmpe  laeveenkkm  sqpgspspkt  ptpstpgdtq  pntpapvppa
1561 edgikieens  lkeeesiege  kevkstapet  aiectqapap  asedekvvve  ppegeekvek
1621 aevkerteep  metepkgaad  vekveeksai  dltpivvedk  eekkeeeekk  evmlqngetp
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1681 kdlndekqkk  nikqrfmfni  adggftelhs  lwqneeraat  vtkktyeiwh  rrhdywllag

1741 iinhgyarwq  diqndpryai  lnepfkgemn  rgnfleiknk  flarrfklle  qalvieeqlr

1801 raaylnmsed  pshpsmalnt  rfaeveclae  shqhlskesm  agnkpanavl  hkvlkqleel

1861 lsdmkadvtr  lpatiaripp  vavrlqmser  nilsrlanra  peptpqqvaq  qq
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[**0072**] IL. Peripheral Benzodiazepine Receptor-Associated Protein 1

[**0073**] Peripheral benzodiazepine receptor-associated protein 1 has been identified as an Akt substrate that interacts with Akt. This protein is associated with reference sequence NP_004749 (GenBank Accession No. 4758956). A specific sequence identified as an Akt substrate includes a hypothetical protein, similar to peripheral benzodiazepine receptor associated protein 1 and RIM-binding protein 1 (KIAA0612) (GenBank Accession No. 7513043).

HP 004749. peripheral benzodiazepine receptor-associated protein 1 [gi: 4758956]	
LOCUS	NP_004749 1857 aa linear PRI 06-OCT-2003
DEFINITION	peripheral benzodiazepine receptor-associated protein 1 [*Homo sapiens*].
ACCESSION	NP_004749
VERSION	NP_004749.1 GI: 4758956
DBSOURCE	REFSEQ: accession NM 004758.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 1857)
AUTHORS	Galiegue, S., Jbilo, O., Combes, T., Bribes, E., Carayon, P., Le Fur, G. and Casellas, P.
TITLE	Cloning and characterization of PRAX-1. A new protein that specifically interacts with the peripheral benzodiazepine receptor
JOURNAL	J. Biol. Chem. 274 (5), 2938–2952 (1999)
MEDLINE	99115641
PUBMED	9915832
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final
NCBI	review. The reference sequence was derived from AF039571.1.
FEATURES	Location/Qualifiers
source	1 . . . 1857 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="17" /map="17q22–q23"
Protein	1 . . . 1857 /product="peripheral benzodiazepine receptor-associated protein 1"
Region	125 . . . 464 /region_name="Chromosome segregation ATPases [Cell division and chromosome partitioning]" /note="Smc" /db_xref="CDD:COG1196"
variation	514 /allele="Q" /allele="R" /db_xref="dbSNP:2072145"
variation	586 /allele="A" /allele="T" /db_xref="dbSNP:2072147"
Region	660 . . . 718 /region name="Src homology 3 domains" /note="SH3" /db_xref="CDD:smart00326"
Region	885 . . . 947 /region name="Fibronectin type 3 domain" /note="FN3" /db_xref="CDD:smart00060"

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HP 004749. peripheral benzodiazepine receptor-associated protein 1 [gi: 4758956]	
variation	1118 /allele="H" /allele="L" /db_xref="dbSNP:3744099"
variation	1140 /allele="P" /allele="A" /db_xref="dbSNP:2680704"
variation	1253 /allele="R" /allele="C" /db_xref="dbSNP:3744101"
Region	1626 . . . 1691 /region name="Src homology 3 domains" /note="SH3" /db_xref="CDD:smart00326"
Region	1766 . . . 1827 /region name="Src homology 3 domains" /note="SH3" /db_xref="CDD:smart00326"
variation	1830 /allele="G" /allele="E" /db_xref="dbSNP:2301868"
CDS	1 . . . 1857 /gene="BZRAP1" /coded_by="NM_004758.1:198..5771" /note="go_component: mitochondrion [goid 0005739] [evidence IDA] [pmid 9915832]; go function: receptor activity [goid 0004872] [evidence IEA]; go function: benzodiazepine receptor binding [goid 0030156] [evidence IPI] [pmid 9915832]; go_process: biological_process unknown [goid 0000004] [evidence ND]" /db_xref="GeneID:9256" /db_xref="LocusID:9256"

[**0074**] Origin

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   1 meqlttlprp  gdpgamepwa  lptwhswtpg  rggepssaap  siadtppaal  qlqelrsees  [SEQ ID NO:21]
  61 skpkgdgssr  pvggtdpega  eaclpslgqq  asssgpacqr  pedeeveafl   kaklnmsfgd
 121 rpnlellral  gelrqrcail  keenqmlrks  sfpeteekvr  rlkrknaela  viakrleera
 181 rklqetnlrv  vsaplprpgt  slelcrkala  rqrardlset  asallakdkq  iaalqrecre
 241 lqarltlvgk  egpqwlhvrd  fdrllresqr  evlrlqrqia  lrnqretlpl  ppswppgpal
 301 qaragapapg  apgeatpqed  adnlpvilge  pekeqrvqql  eselskkrkk  cesleqeark
 361 kqrrceelel  qlrqaqnena  rlveensrls  gratekeqve  wenaelrgql  lgvtqerdsa
 421 lrksqglqsk  lesleqvlkh  mrevaqrrqq  leveheqarl  slrekqeevr  rlqqaqaeaq
 481 rehegavqll  estldsmqar  vreleeqcrs  qteqfsllaq  elqafrlhpg  pldlltsald
 541 cgslgdcppp  pcccsipqpc  rgsgpkdldl  ppgspgrctp  kssepapatl  tgvprrtakk
 601 aeslsnsshs  esihnspksc  ptpevdtase  veeleadsvs  llpaapegsr  ggariqvfla
 661 rysynpfegp  nenpeaelpl  tageyiyiyg  nmdedgffeg  elmdgrrglv  psnfvervsd
 721 ddlltslppe  ladlshssgp  elsflsvggg   gsssgggssv  grsqprpeee  dagdelslsp
 781 speglgeppa  vpyprrlvvl  kqlahsvvla  wepppeqvel  hgfhicvnge  lrqalgpgap
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 841 pkavlenldl  wagplhisvq  altsrgssdp  lrcclavgar  agvvpsqlrv  hrltatsaei

 901 twvpgnsnla  haiylngeec  ppaspstywa  tfchlrpgtp  yqaqveaqlp  pqgpwepgwe

 961 rleqraatlq  fttlpagppd  apldvqiepg  pspgiliisw  lpvtidaagt  sngvrvtgya

1021 iyadgqkime  vasptagsvl  velsqlqllq  vcrevvvrtm  sphgesadsi  papitpalap

1081 aslparvscp  sphpspeara  plasaspgpg  dpssplqhpa  plgtqeppga  ppaspsrema

1141 kgshedppap  csqeeagaav  lgtseertas  tstlgekdpg  paapslakqe  aewtageacp

1201 assstqgara  qqapntemcq  ggdpgsglrp  raekedtael  gvhlvnslvd  hgrnsdlsdi

1261 qeeeeeeeee  eeeelgsrtc  sfqkqvagns  irengaksqp  dpfcetdsde  eileqilelp

1321 lqqfcskklf  sipeeeeeee  edeeeeksga  gcssrdpgpp  epallglgcd  sgqprrpgqc

1381 plspessrag  dcledmpglv  ggssrrrggg  spekppsrrr  ppdprehcsr  llsnngpqas

1441 grlgptrerg  glpviegprt  gleasgrgrl  gpsrrcsrgr  alepglascl  spkcleisie

1501 ydsedeqeag  sggisitssc  ypgdreawgt  atvgrprgpp  kansgpkpyp  rlpawekgep

1561 errgrsatgr  akeplsrate  tgeargqdgs  grrgpqkrgv  rvlrpstael  vparspsetl

1621 ayqhlpvrif  valfdydpvs  mspnpdagee  elpfregqil  kvfgdkdadg  fyqgegggrt

1681 gyipcnmvae  vavdspagrq  qllqrgylsp  dillegsgng  pfvystahtt  gpppkprrsk

1741 kaesegpaqp  cpgppklvps  adlkaphsmv  aafdynpqes  spnmdveael  pfragdvitv

1801 fggmdddgfy  ygelngqrgl  vpsnflegpg  peaggidrep  rtpqaesqrt  rrrrvqc
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[0075] IM. Heterogeneous Nuclear Ribonucleoprotein U (Scaffold Attachment Factor A (hnRNP U Protein)

[0076] Heterogeneous Nuclear Ribonucleoprotein U (Scaffold Attachment Factor A) (hnRNP U) protein has been identified as an Akt substrate that interacts with Akt. Human hnRNP U includes isoform a, associated with reference sequence NP_114032 (GenBank Accession No. 14141163) and isoform b, associated with reference sequence NP_004492 (GenBank Accession No. 14141161). A specific sequence identified as an Akt substrate includes a protein similar to hnRNP U (GenBank Accession No. 14044052).

NP_004492. heterogeneous nuclear ribonucleoprotein U isoform b [gi: 14141161]

LOCUS	NP_004492 806 aa linear PRI 05-OCT-2003
DEFINITION	heterogeneous nuclear ribonucleoprotein U isoform b; hnRNP U protein; scaffold attachment factor A; p120 nuclear protein [*Homo sapiens*].
ACCESSION	NP_004492
VERSION	NP_004492.2 GI: 14141161
DBSOURCE	REFSEQ: accession NM 004501.2
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 806)
AUTHORS	Martens, J. H., Verlaan, M., Kalkhoven, E., Dorsman, J. C. and Zantema, A.
TITLE	Scaffold/matrix attachment region elements interact with a p300-scaffold attachment factor A complex and are bound by acetylated nucleosomes
JOURNAL	Mol. Cell. Biol. 22 (8), 2598–2606 (2002)
MEDLINE	21907223
PUBMED	11909954
REMARK	GeneRIF: Scaffold/matrix attachment region elements interact with a p300-scaffold attachment factor A complex and are bound by acetylated nucleosomes.
REFERENCE	2 (residues 1 to 806)
AUTHORS	Davis, M., Hatzubai, A., Andersen, J. S., Ben-Shushan, E., Fisher, G. Z., Yaron, A., Bauskin, A., Mercurio, F., Mann, M. and Ben-Neriah, Y.

-continued

NP_004492. heterogeneous nuclear ribonucleoprotein U isoform b [gi: 14141161]

TITLE	Pseudosubstrate regulation of the SCF(beta-TrCP) ubiquitin ligase by hnRNP-U
JOURNAL	Genes Dev. 16 (4), 439–451 (2002)
MEDLINE	21838685
PUBMED	11850407
REMARK	GeneRIF: hnRNP-U engages a highly neddlylated active SCF beta-TRCP which dissociates in the presence of a high-affinity substrate, resulting in the ubiquitination of the latter.
REFERENCE	3 (residues 1 to 806)
AUTHORS	Kipp, M., Schwab, B. L., Przybylski, M., Nicotera, P. and Fackelmayer, F. O.
TITLE	Apoptotic cleavage of scaffold attachment factor A (SAF-A) by caspase-3 occurs at a noncanonical cleavage site
JOURNAL	J. Biol. Chem. 275 (7), 5031–5036 (2000)
MEDLINE	20138248
PUBMED	10671544
REFERENCE	4 (residues 1 to 806)
AUTHORS	Gohring, F., Schwab, B. L., Nicotera, P., Leist, M. and Fackelmayer, F. O.
TITLE	The novel SAR-binding domain of scaffold attachment factor A
(SAF-A)	is a target in apoptotic nuclear breakdown
JOURNAL	EMBO J. 16 (24), 7361–7371 (1997)
MEDLINE	98070313
PUBMED	9405365
REFERENCE	5 (residues 1 to 806)
AUTHORS	Fackelmayer, F. O. and Richter, A.
TITLE	Purification of two isoforms of hnRNP-U and characterization of their nucleic acid binding activity
JOURNAL	Biochemistry 33 (34), 10416–10422 (1994)
MEDLINE	94347778
PUBMED	8068679
REFERENCE	6 (residues 1 to 806)
AUTHORS	Fackelmayer, F. O. and Richter, A.
TITLE	hnRNP-U/SAF-A is encoded by two differentially polyadenylated mRNAs in human cells
JOURNAL	Biochim. Biophys. Acta 1217 (2), 232–234 (1994)
MEDLINE	94154006
PUBMED	7509195
REFERENCE	7 (residues 1 to 806)
AUTHORS	Kiledjian, M. and Dreyfuss, G.
TITLE	Primary structure and binding activity of the hnRNP U protein: binding RNA through RGG box
JOURNAL	EMBO J. 11 (7), 2655–2664 (1992)
MEDLINE	92331618
PUBMED	1628625
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from BC003367.1 and AF068846.1. On May 17, 2001 this sequence version replaced gi: 4758546. Summary: This gene belongs to the subfamily of ubiquitously expressed heterogeneous nuclear ribonucleoproteins (hnRNPs). The hnRNPs are RNA binding proteins and they complex with heterogeneous nuclear RNA (hnRNA). These proteins are associated with pre-mRNAs in the nucleus and appear to influence pre-mRNA processing and other aspects of mRNA metabolism and transport. While all of the hnRNPs are present in the nucleus, some seem to shuttle between the nucleus and the cytoplasm. The hnRNP proteins have distinct nucleic acid binding properties. The protein encoded by this gene contains a RNA binding domain and scaffold-associated region (SAR)-specific bipartite DNA-binding domain. This protein is also thought to be involved in the packaging of hnRNA into large ribonucleoprotein complexes. During apoptosis, this protein is cleaved in a caspase-dependent way. Cleavage occurs at the SALD site, resulting in a loss of DNA-binding activity and a concomitant detachment of this protein from nuclear structural sites. But this cleavage does not affect the function of the encoded protein in RNA metabolism. Two alternatively spliced transcript variants have been described for this gene. Transcript Variant: This variant (2) lacks 54 bases in the coding region compared to variant 1. This causes the isoform b to be 18 amino acids shorter than isoform a, but it maintains the same reading frame.

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NP_004492. heterogeneous nuclear ribonucleoprotein U isoform b [gi: 14141161]

FEATURES	Location/Qualifiers
source	1 . . . 806 /organism="*Homo sapiens*" /db_xref="taxon: 9606" /chromosome="1" /map="1q44"
Protein	1 . . . 806 /product="heterogeneous nuclear ribonucleoprotein U isoform b" /note="hnRNP U protein; scaffold attachment factor A; p120 nuclear protein"
Region	100 /region name="SALD cleavage site"
Region	328 . . . 444 /region_name="SPRY domain. SPRY Domain is named from SPla and the RY anodine Receptor. Domain of unknown function. Distant homologues are domains in butyrophilin/marenostrin/pyrin homologues" /note="SPRY" /db_xref="CDD:pfam00622"
Region	480 . . . 630 /region_name="COG4639, Predicted kinase [General function prediction only]" /note="COG4639" /db_xref="CDD:COG4639"
variation	693 /allele="F" /allele="L" /db_xref="dbSNP: 1052660"
CDS	1 . . . 806 /gene="HNRPU" /coded_by="NM_004501.2:219..2639" /note="go component: nucleoplasm [goid 0005654] [evidence NR]; go_component: nucleus [goid 0005634] [evidence NR]; go component: ribonucleoprotein complex [goid 0030529] [evidence IEA]; go function: heterogeneous nuclear ribonucleoprotein [goid 0008436] [evidence TAS] [pmid 7509195]; go function: RNA binding [goid 0003723] [evidence TAS] [pmid 1628625]; go function: DNA binding [goid 0003677] [evidence TAS] [pmid 1628625]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_process: RNA processing [goid 0006396] [evidence TAS] [pmid 1628625]" /db_xref="GeneID:3192" /db_xref="LocusID:3192" /db_xref="MIM:602869"

[**0077**] Origin

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  1mssspvnvkk lkvselkeel kkrrlsdkgl kaelmerlqa alddeeaggr pamepgngsl [SEQ ID NO:22]

 61dlggdsagrs gagleqeaaa ggdeeeeeee eeeegisald gdqmelgeen gaagaadsgp

121meeeeaased engddqgfqe gedelgdeee gagdenghge qqpqppatqq qqpqqqrgaa

181keaagkssgp tslfavtvap pgarqgqqqa ggdgkteqkg gdkkrgvkrp redhgrgyfe

241yieenkysra kspqppveee dehfddtvvc ldtyncdlhf kisrdrlsas sitmesfafl

301waggrasygv skgkvcfemk vtekipvrhl ytkdidihev rigwslttsg mllgeeefsy

361gyslkgiktc ncetedygek fdendvitcf anfesdevel syakngqdlg vafkiskevl

421agrplfphvl chncavefnf gqkekpyfpi peeytfiqnv pledrvrgpk gpeekkdcev

481vmmiglpgag kttwvtkhaa enpgkynilg tntimdkmmv agfkkqmadt gklntllqra
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541pqclgkfiei  aarkkrnfil  dqtnvsaaaq  rrkmclfagf  qrkavvvcpk  dedykqrtqk

601kaevegkdlp  ehavlkmkgn  ftlpevaecf  deityvelqk  eeaqkllegy  keeskkalpp

661ekkqntgskk  snknksgknq  fnrggghrgr  ggfnmrggnf  rggapgnrgg  ynrrgnmpqr

721ggggggsggi  gypyprapvf  pgrgsysnrg  nynrggmpnr  gnynqnfrgr  gnnrgyknqs

781qgynqwgggq  fwgqkpwsqh  yhqgyy
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[0078]

NP_114032. heterogeneous nuclear ribonucloeprotein U isoform a

LOCUS	NP_114032 824 aa linear PRI 05-OCT-2003
DEFINITION	heterogeneous nuclear ribonucleoprotein U isoform a; hnRNP U protein; scaffold attachment factor A; p120 nuclear protein [*Homo sapiens*].
ACCESSION	NP_114032
VERSION	NP_114032.1 GI: 14141163
DBSOURCE	REFSEQ: accession NM_031844.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 824)
AUTHORS	Martens, J. H., Verlaan, M., Kalkhoven, E., Dorsman, J. C. and Zantema, A.
TITLE	Scaffold/matrix attachment region elements interact with a p300-scaffold attachment factor A complex and are bound by acetylated nucleosomes
JOURNAL	Mol. Cell. Biol. 22 (8), 2598–2606 (2002)
MEDLINE	21907223
PUBMED	11909954
REMARK	GeneRIF: Scaffold/matrix attachment region elements interact with a p300-scaffold attachment factor A complex and are bound by acetylated nucleosomes.
REFERENCE	2 (residues 1 to 824)
AUTHORS	Davis, M., Hatzubai, A., Andersen, J. S., Ben-Shushan, E., Fisher, G. Z., Yaron, A., Bauskin, A., Mercurio, F., Mann, M. and Ben-Neriah, Y.
TITLE	Pseudosubstrate regulation of the SCF(beta-TrCP) ubiquitin ligase by hnRNP-U
JOURNAL	Genes Dev. 16 (4), 439–451 (2002)
MEDLINE	21838685
PUBMED	11850407
REMARK	GeneRIF: hnRNP-U engages a highly neddlylated active SCF beta-TRCP which dissociates in the presence of a high-affinity substrate, resulting in the ubiquitination of the latter.
REFERENCE	3 (residues 1 to 824)
AUTHORS	Kipp, M., Schwab, B. L., Przybylski, M., Nicotera, P. and Fackelmayer, F. O.
TITLE	Apoptotic cleavage of scaffold attachment factor A (SAF-A) by caspase-3 occurs at a noncanonical cleavage site
JOURNAL	J. Biol. Chem. 275 (7), 5031–5036 (2000)
MEDLINE	20138248
PUBMED	10671544
REFERENCE	4 (residues 1 to 824)
AUTHORS	Gohring, F., Schwab, B. L., Nicotera, P., Leist, M. and Fackelmayer, F.O.
TITLE	The novel SAR-binding domain of scaffold attachment factor A (SAF-A) is a target in apoptotic nuclear breakdown
JOURNAL	EMBO J. 16 (24), 7361–7371 (1997)
MEDLINE	98070313
PUBMED	9405365
REFERENCE	5 (residues 1 to 824)
AUTHORS	Fackelmayer, F. O. and Richter, A.
TITLE	Purification of two isoforms of hnRNP-U and characterization of their nucleic acid binding activity
JOURNAL	Biochemistry 33 (34), 10416–10422 (1994)
MEDLINE	94347778
PUBMED	8068679
REFERENCE	6 (residues 1 to 824)

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NP_114032. heterogeneous nuclear ribonucloeprotein U isoform a

AUTHORS	Fackelmayer, F. O. and Richter, A.
TITLE	hnRNP-U/SAF-A is encoded by two differentially polyadenylated mRNAs in human cells
JOURNAL	Biochim. Biophys. Acta 1217 (2), 232–234 (1994)
MEDLINE	94154006
PUBMED	7509195
REFERENCE	7 (residues 1 to 824)
AUTHORS	Kiledjian, M. and Dreyfuss, G.
TITLE	Primary structure and binding activity of the hnRNP U protein: binding RNA through RGG box
JOURNAL	EMBO J. 11 (7), 2655–2664 (1992)
MEDLINE	92331618
PUBMED	1628625
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AF068846.1. Summary: This gene belongs to the subfamily of ubiquitously expressed heterogeneous nuclear ribonucleoproteins (hnRNPs). The hnRNPs are RNA binding proteins and they complex with heterogeneous nuclear RNA (hnRNA). These proteins are associated with pre-mRNAs in the nucleus and appear to influence pre-mRNA processing and other aspects of mRNA metabolism and transport. While all of the hnRNPs are present in the nucleus, some seem to shuttle between the nucleus and the cytoplasm. The hnRNP proteins have distinct nucleic acid binding properties. The protein encoded by this gene contains a RNA binding domain and scaffold-associated region (SAR)-specific bipartite DNA-binding domain. This protein is also thought to be involved in the packaging of hnRNA into large ribonucleoprotein complexes. During apoptosis, this protein is cleaved in a caspase-dependent way. Cleavage occurs at the SALD site, resulting in a loss of DNA-binding activity and a concomitant detachment of this protein from nuclear structural sites. But this cleavage does not affect the function of the encoded protein in RNA metabolism. Two alternatively spliced transcript variants have been described for this gene. Transcript Variant: This variant (1) encodes the full length isoform.
FEATURES	Location/Qualifiers
source	1 . . . 824 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="1" /map="1q44"
Protein	1 . . . 824 /product="heterogeneous nuclear ribonucleoprotein U isoform a" /note="hnRNP U protein; scaffold attachment factor A; p120 nuclear protein"
Region	100 /region_name="SALD cleavage site"
misc_feature	213 . . . 230 /note="glycine-rich region"
Region	346 . . . 462 /region_name="SPRY domain. SPRY Domain is named from SPla and the RY anodine Receptor. Domain of unknown function. Distant homologues are domains in butyrophilin/marenostrin/pyrin homologues" /note="SPRY" /db_xref="CDD:pfam00622"
Region	498 . . . 648 /region_name="COG4639, Predicted kinase [General function prediction only]" /note="COG4639" /db_xref="CDD:COG4639"
variation	711 /allele="F" /allele="L" /db_xref="dbSNP:1052660"
CDS	1 . . . 824 /gene="HNRPU" /coded_by="NM_031844.1:218..2692" /note="go_component: nucleoplasm [goid 0005654] [evidence NR];

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NP_114032. heterogeneous nuclear ribonucloeprotein U isoform a
go_component: nucleus [goid 0005634] [evidence NR]; go_component: ribonucleoprotein complex [goid 0030529] [evidence IEA]; go_function: heterogeneous nuclear ribonucleoprotein [goid 0008436] [evidence TAS] [pmid 7509195]; go_function: RNA binding [goid 0003723] [evidence TAS] [pmid 1628625]; go_function: DNA binding [goid 0003677] [evidence TAS] [pmid 1628625]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_process: RNA processing [goid 0006396] [evidence TAS] [pmid 1628625]" /db_xref="GeneID:3192" /db_xref="LocusID:3192" /db_xref="MIM:602869"

[0079] Origin

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  1mssspvnvkk lkvselkeel kkrrlsdkgl kaelmerlqa alddeeaggr pamepgngsl [SEQ ID NO:23]

 61dlggdsagrs gagleqeaaa ggdeeeeeee eeeegisald gdqmelgeen gaagaadsgp

121meeeeaased engddqgfqe gedelgdeee gagdenghge qqpqppatqq qqpqqqrgaa

181keaagkssgp tslfavtvap pgarqgqqqa ggkkkaeggg gggrpgapag dgkteqkggd

241kkrgvkrpre dhgrgyfeyi eenkysraks pqppveeede hfddtvvcld tyncdlhfki

301srdrlsassl tmesfaflwa  ggrasygvsk gkvcfemkvt ekipvrhlyt kdidihevri

361gwslttsgml lgeeefsygy slkgiktcnc etedygekfd endvitcfan fesdevelsy

421akngqdlgva fkiskevlag rplfphvlch ncavefnfgq kekpyfpipe eytfiqnvpl

481edrvrgpkgp eekkdcevvm miglpgagkt twvtkhaaen pgkynilgtn timdkmmvag

541fkkqmadtgk lntllqrapq clgkfieiaa  rkkrnfildq  tnvsaaaqrr kmclfagfqr

601kavvvcpkde dykqrtqkka evegkdlpeh avlkmkgnft lpevaecfde ityvelqkee

661aqkllegyke eskkalppek kqntgskksn knksgkngfn rggghrgrgg lnmrggnfrg

721gapgnrggyn rrgnmpgrgg ggggsggigy pyprapvfpg rgsysnrgny nrggmpnrgn

781ynqnfrgrgn nrgyknqsqg ynqwqqgqfw gqkpwsqhyh qgyy
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[0080] IN. Pyruvate Carboxylase

[0081] Pyruvate carboxylase has been identified as an Akt substrate that interacts with Akt. Human pyruvate carboxylase is associated with reference sequence NP_000911 (GenBank Accession No. 4505627) and reference sequence NP_0071504 (GenBank Accession No. 11761615). Other relevant sequences include mouse pyruvate carboxylase (GenBank Accession No. 200246).

NP_000911. pyruvate carboxylase [gi: 4505627]	
LOCUS	NP_000911 1178 aa linear PRI 04-OCT-2003
DEFINITION	pyruvate carboxylase precursor [*Homo sapiens*].
ACCESSION	NP_000911
VERSION	NP_000911.1 GI: 4505627
DBSOURCE	REFSEQ: accession NM_000920.2
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.

-continued

NP_000911. pyruvate carboxylase [gi: 4505627]

REFERENCE	1 (residues 1 to 1178)
AUTHORS	Carbone, M. A. and Robinson, B. H.
TITLE	Expression and characterization of a human pyruvate carboxylase variant by retroviral gene transfer
JOURNAL	Biochem. J. 370 (Pt 1), 275–282 (2003)
MEDLINE	22458341
PUBMED	12437512
REMARK	GeneRIF: expression and characterization of a variant by retroviral gene transfer
REFERENCE	2 (residues 1 to 1178)
AUTHORS	Carbone, M. A., Applegarth, D. A. and Robinson, B. H.
TITLE	Intron retention and frameshift mutations result in severe pyruvate carboxylase deficiency in two male siblings
JOURNAL	Hum. Mutat. 20 (1), 48–56 (2002)
MEDLINE	22106101
PUBMED	12112657
REMARK	GeneRIF: IVS15+2-5delTAGG results in the retention of intron 15 during pre-mRNA splicing and frameshift mutations.
REFERENCE	3 (residues 1 to 1178)
AUTHORS	Jitrapakdee, S. and Wallace, J. C.
TITLE	Structure, function and regulation of pyruvate carboxylase
JOURNAL	Biochem. J. 340 (Pt 1), 1–16 (1999)
MEDLINE	99247890
PUBMED	10229653
REFERENCE	4 (residues 1 to 1178)
AUTHORS	Wallace, J. C., Jitrapakdee, S. and Chapman-Smith, A.
TITLE	Pyruvate carboxylase
JOURNAL	Int. J. Biochem. Cell Biol. 30 (1), 1–5 (1998)
MEDLINE	98260036
PUBMED	9597748
REFERENCE	5 (residues 1 to 1178)
AUTHORS	Walker, M. E., Baker, E., Wallace, J. C. and Sutherland, G. R.
TITLE	Assignment of the human pyruvate carboxylase gene (PC) to 11q13.4 by fluorescence in situ hybridisation
JOURNAL	Cytogenet. Cell Genet. 69 (3–4), 187–189 (1995)
MEDLINE	95212152
PUBMED	7698008
REFERENCE	6 (residues 1 to 1178)
AUTHORS	Wexler, I. D., Du, Y., Lisgaris, M. V., Mandal, S. K., Freytag, S. O., Yang, B. S., Liu, T. C, Kwon, M., Patel, M. S. and Kerr, D. S.
TITLE	Primary amino acid sequence and structure of human pyruvate carboxylase
JOURNAL	Biochim. Biophys. Acta 1227 (1–2), 46–52 (1994)
MEDLINE	95002202
PUBMED	7918683
REFERENCE	7 (residues 1 to 1178)
AUTHORS	MacKay, N., Rigat, B., Douglas, C., Chen, H. S. and Robinson, B. H.
TITLE	cDNA cloning of human kidney pyruvate carboxylase
JOURNAL	Biochem. Biophys. Res. Commun. 202 (2), 1009–1014 (1994)
MEDLINE	94324922
PUBMED	8048912
REFERENCE	8 (residues 1 to 1178)
AUTHORS	Lamhonwah, A. M., Quan, F. and Gravel, R. A.
TITLE	Sequence homology around the biotin-binding site of human propionyl-CoA carboxylase and pyruvate carboxylase
JOURNAL	Arch. Biochem. Biophys. 254 (2), 631–636 (1987)
MEDLINE	87212051
PUBMED	3555348
REFERENCE	9 (residues 1 to 1178)
AUTHORS	Freytag, S. O. and Collier, K. J.
TITLE	Molecular cloning of a cDNA for human pyruvate carboxylase. Structural relationship to other biotin-containing carboxylases and regulation of mRNA content in differentiating preadipocytes
JOURNAL	J. Biol. Chem. 259 (20), 12831–12837 (1984)
MEDLINE	85030380
PUBMED	6548474
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from U30891.1 and U30889.1. Summary: This gene encodes pyruvate carboxylase, which requires biotin and ATP to catalyse the carboxylation of pyruvate to oxaloacetate. The active enzyme is a homotetramer arranged in a tetrahedron which is located exclusively in the mitochondrial matrix. Pyruvate carboxylase is involved in gluconeogenesis, lipogenesis, insulin secretion and synthesis of the

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NP_000911. pyruvate carboxylase [gi: 4505627]	
	neurotransmitter glutamate. Mutations in this gene have been associated with pyruvate carboxylase deficiency. Two transcript variants are encoded by this gene. Transcript Variant: This variant (A) encodes a 5' UTR which is longer and different from that found in transcript variant B. Both variants encode the same protein sequence.
FEATURES	Location/Qualifiers
source	1 . . . 1178 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="11" /map="11q13.4–q13.5"
Protein	1 . . . 1178 /product="pyruvate carboxylase precursor" /EC_number="6.4.1.1"
transit peptide	1 . . . 20 /note="mitochondrial targeting sequence"
mat peptide	21 . . . 1178 /product="pyruvate carboxylase" /EC_number="6.4.1.1"
Region	35 . . . 1178 /region_name="Pyruvate carboxylase [Energy production and conversion]" /note="PycA" /db_xref="CDD:COG1038"
variation	76 /allele="H" /allele="L" /db_xref="dbSNP:7104156"
variation	352 /allele="A" /allele="S" /db_xref="dbSNP:1051704"
CDS	1 . . . 1178 /gene="PC" /coded_by="NM_000920.2:202..3738" /note="go_component: mitochondrion [goid 0005739] [evidence NR]; go_function: pyruvate carboxylase activity [goid 0004736] [evidence TAS] [pmid 7918683]; go_function: biotin binding [goid 0009374] [evidence TAS] [pmid 8048912]; go_function: ATP binding [goid 0005524] [evidence TAS] [pmid 8048912]; go_function: ligase activity [goid 0016874] [evidence IEA]; go_function: manganese ion binding [goid 0030145] [evidence IEA]; go_process: biotin metabolism [goid 0006768] [evidence IEA]; go_process: gluconeogenesis [goid 0006094] [evidence IEA]; go_process: metabolism [goid 0008152] [evidence IEA]; go_process: lipid biosynthesis [goid 0008610] [evidence IEA]" /db_xref="GeneID:5091" /db_xref="LocusID:5091" /db_xref="MIM:266150"

[**0082**] Origin

```
   1 mlkfrtvhgg  lrllgirrts  tapaaspnvr  rleykpikkv  mvanrgeiai  rvfractelg  [SEQ ID NO:24]

  61 irtvaiyseq  dtgqmhrqka  deayligrgl  apvqaylhip  diikvakenn  vdavhpgygf

 121 lseradfaqa  cqdagvrfig  pspevvrkmg  dkvearaiai  aagvpvvpgt  dapitslhea

 181 hefsntygfp  iifkaayggg  grgmrvvhsy  eeleenytra  ysealaafgn  galfvekfie

 241 kprhievqil  gdqygnilhl  yerdcsiqrr  hqkvveiapa  ahldpqlrtr  ltsdsvklak
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 301 qvgyenagtv  eflvdrhgkh  yfievnsrlq  vehtvteeit  dvdlvhaqih  vsegrslpdl
 361 glrqenirin  gcaiqcrvtt  edparsfqpd  tgrievfrsg  egmgirldna  safqgavisp
 421 hydsllvkvi  ahgkdhptaa  tkmsralaef  rvrgvktnia  flqnvlnnqq  flagtvdtqf
 481 idenpelfql  rpaqnraqkl  lhylghvmvn  gpttpipvka  spsptdpvvp  avpigpppag
 541 frdillregp  egfaravrnh  pglllmdttf  rdahqsllat  rvrthdlkki  apyvahnfsk
 601 lfsmenwgga  tfdvamrfly  ecpwrrlqel  relipnipfq  mllrganavg  ytnypdnvvf
 661 kfcevakeng  mdvfrvfdsl  nylpnmllgm  eaagsaggvv  eaaisytgdv  adpsrtkysl
 721 qyymglaeel  vragthilci  kdmagllkpt  actmlvsslr  drfpdlplhi  hthdtsgagv
 781 aamlacaqag  advvdvaads  msgmtsqpsm  galvactrgt  pldtevpmer  vfdyseyweg
 841 arglyaafdc  tatmksgnsd  vyeneipggq  ytnlhfqahs  mglgskfkev  kkayveanqm
 901 lgdlikvtps  skivgdlaqf  mvqnglsrae  aeaqaeelsf  prsvveflqg  yigvphggfp
 961 epfrskvlkd  lprvegrpga  sippidiqal  ekelvdrhge  evtpedvlsa  amypdvfahf
1021 kdftatfgpl  dslntrlflq  gpkiaeefev  elergktlhi  kalavsdlnr  agqrqvffel
1081 ngqlrsilvk  dtqamkemhf  hpkalkdvkg  qigapmpgkv  idikvvagak  vakgqplcvl
1141 samkmetvvt  spmegtvrkv  hvtkdmtleg  ddlileie
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[0083]

NP_071504. pyruvate carboxylase precursor [gi: 11761615]	
LOCUS	NP_071504 1178 aa linear PRI 05-OCT-2003
DEFINITION	pyruvate carboxylase precursor [*Homo sapiens*].
ACCESSION	NP_071504
VERSION	NP_071504.1 GI: 11761615
DBSOURCE	REFSEQ: accession NM_022172.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 1178)
AUTHORS	Carbone, M. A. and Robinson, B. H.
TITLE	Expression and characterization of a human pyruvate carboxylase variant by retroviral gene transfer
JOURNAL	Biochem. J. 370 (Pt 1), 275–282 (2003)
MEDLINE	22458341
PUBMED	12437512
REMARK	GeneRIF: expression and characterization of a variant by retroviral gene transfer
REFERENCE	2 (residues 1 to 1178)
AUTHORS	Carbone, M. A., Applegarth, D. A. and Robinson, B. H.
TITLE	Intron retention and frameshift mutations result in severe pyruvate carboxylase deficiency in two male siblings
JOURNAL	Hum. Mutat. 20 (1), 48–56 (2002)
MEDLINE	22106101
PUBMED	12112657
REMARK	GeneRIF: IVS15+2-5delTAGG results in the retention of intron 15 during pre-mRNA splicing and frameshift mutations.
REFERENCE	3 (residues 1 to 1178)
AUTHORS	Jitrapakdee, S. and Wallace, J. C.
TITLE	Structure, function and regulation of pyruvate carboxylase
JOURNAL	Biochem. J. 340 (Pt 1), 1–16 (1999)
MEDLINE	99247890
PUBMED	10229653

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NP_071504. pyruvate carboxylase precursor [gi: 11761615]

REFERENCE	4 (residues 1 to 1178)
AUTHORS	Wallace, J. C., Jitrapakdee, S. and Chapman-Smith, A.
TITLE	Pyruvate carboxylase
JOURNAL	Int. J. Biochem. Cell Biol. 30 (1), 1–5 (1998)
MEDLINE	98260036
PUBMED	9597748
REFERENCE	5 (residues 1 to 1178)
AUTHORS	Walker, M. E., Baker, E., Wallace, J. C. and Sutherland, G. R.
TITLE	Assignment of the human pyruvate carboxylase gene (PC) to 11q13.4 by fluorescence in situ hybridisation
JOURNAL	Cytogenet. Cell Genet. 69 (3–4), 187–189 (1995)
MEDLINE	95212152
PUBMED	7698008
REFERENCE	6 (residues 1 to 1178)
AUTHORS	Wexler, I. D., Du, Y., Lisgaris, M. V., Mandal, S. K., Freytag, S. O., Yang, B. S., Liu, T. C., Kwon, M., Patel, M. S. and Kerr, D. S.
TITLE	Primary amino acid sequence and structure of human pyruvate carboxylase
JOURNAL	Biochim. Biophys. Acta 1227 (1–2), 46–52 (1994)
MEDLINE	95002202
PUBMED	7918683
REFERENCE	7 (residues 1 to 1178)
AUTHORS	MacKay, N., Rigat, B., Douglas, C., Chen, H. S. and Robinson, B. H.
TITLE	cDNA cloning of human kidney pyruvate carboxylase
JOURNAL	Biochem. Biophys. Res. Commun. 202 (2), 1009–1014 (1994)
MEDLINE	94324922
PUBMED	8048912
REFERENCE	8 (residues 1 to 1178)
AUTHORS	Lamhonwah, A. M., Quan, F. and Gravel, R. A.
TITLE	Sequence homology around the biotin-binding site of human propionyl-CoA carboxylase and pyruvate carboxylase
JOURNAL	Arch. Biochem. Biophys. 254 (2), 631–636 (1987)
MEDLINE	87212051
PUBMED	3555348
REFERENCE	9 (residues 1 to 1178)
AUTHORS	Freytag, S. O. and Collier, K. J.
TITLE	Molecular cloning of a cDNA for human pyruvate carboxylase. Structural relationship to other biotin-containing carboxylases and regulation of mRNA content in differentiating preadipocytes
JOURNAL	J. Biol. Chem. 259 (20), 12831–12837 (1984)
MEDLINE	85030380
PUBMED	6548474
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from U30891.1 and U30890.1. Summary: This gene encodes pyruvate carboxylase, which requires biotin and ATP to catalyse the carboxylation of pyruvate to oxaloacetate. The active enzyme is a homotetramer arranged in a tetrahedron which is located exclusively in the mitochondrial matrix. Pyruvate carboxylase is involved in gluconeogenesis, lipogenesis, insulin secretion and synthesis of the neurotransmitter glutamate. Mutations in this gene have been associated with pyruvate carboxylase deficiency. Two transcript variants are encoded by this gene. Transcript Variant: This variant (2) encodes a 5' UTR which is shorter and different from that found in transcript variant 1. Both variants encode the same protein sequence.
FEATURES	Location/Qualifiers
source	1 . . . 1178 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="11" /map="11q13.4-q13.5"
Protein	1 . . . 1178 /product="pyruvate carboxylase precursor" /EC_number="6.4.1.1"
transit_peptide	1 . . . 20 /note="mitochondrial targeting sequence"
mat_peptide	21 . . . 1178 /product="pyruvate carboxylase" /EC_number="6.4.1.1"

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NP_071504. pyruvate carboxylase precursor [gi: 11761615]	
Region	35 . . . 1178 /region_name="Pyruvate carboxylase [Energy production and conversion]" /note="PycA" /db_xref="CDD:COG1038"
variation	76 /allele="H" /allele="L" /db_xref="dbSNP:7104156"
variation	352 /allele="A" /allele="S" /db_xref="dbSNP:1051704"
CDS	1 . . . 1178 /gene="PC" /coded_by="NM_022172.1:132..3668" /note="go_component: mitochondrion [goid 0005739] [evidence NR]; go_function: pyruvate carboxylase activity [goid 0004736] [evidence TAS] [pmid 7918683]; go_function: biotin binding [goid 0009374] [evidence TAS] [pmid 8048912]; go_function: ATP binding [goid 0005524] [evidence TAS] [pmid 8048912]; go_function: ligase activity [goid 0016874] [evidence IEA]; go_function: manganese ion binding [goid 0030145] [evidence IEA]; go_process: biotin metabolism [goid 0006768] [evidence IEA]; go_process: gluconeogenesis [goid 0006094] [evidence IEA]; go_process: metabolism [goid 0008152] [evidence IEA]; go_process: lipid biosynthesis [goid 0008610] [evidence IEA]" /db_xref="GeneID:5091" /db_xref="LocusID:5091" /db_xref="MIM:266150"

[**0084**] Origin

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   1 mlkfrtvhgg  lrllgirrts  tapaaspnvr  rleykpikkv  mvanrgeiai  rvfractelg  [SEQ ID NO:25]
  61 irtvaiyseq  dtgqmhrqka  deayligrgl  apvqaylhip  diikvakenn  vdavhpgygf
 121 lseradfaqa  cqdagvrfig  pspevvrkmg  dkvearaiai  aagvpvvpgt  dapitslhea
 181 hefsntygfp  iifkaayggg  grgmrvvhsy  eeleenytra  ysealaafgn  galfvekfie
 241 kprhievqil  gdqygnilhl  yerdcsiqrr  hqkvveiapa  ahldpqlrtr  ltsdsvklak
 301 qvgyenagtv  eflvdrhgkh  yfievnsrlq  vehtvteeit  dvdlvhaqih  vsegrslpdl
 361 glrqenirin  gcaiqcrvtt  edparsfqpd  tgrievfrsg  egmgirldna  safqgavisp
 421 hydsllvkvi  ahgkdhptaa  tkmsralaef  rvrgvktnia  flqnvlnnqq  flagtvdtqf
 481 idenpelfql  rpaqnraqkl  lhylghvmvn  gpttpipvka  spsptdpvvp  avpigpppag
 541 frdillregp  egfaravrnh  pglllmdttf  rdahqsllat  rvrthdlkki  apyvahnfsk
 601 lfsmenwgga  tfdvamrfly  ecpwrrlqel  relipnipfq  mllrganavg  ytnypdnvvf
 661 kfcevakeng  mdvfrvfdsl  nylpnmllgm  eaagsaggvv  eaaisytgdv  adpsrtkysl
 721 qyymglaeel  vragthilci  kdmagllkpt  actmlvsslr  drfpdlplhi  hthdtsgagv
 781 aamlacaqag  advvdvaads  msgmtsqpsm  galvactrgt  pldtevpmer  vfdyseyweg
 841 arglyaafdc  tatmksgnsd  vyeneipggq  ytnlhfqahs  mglgskfkev  kkayveanqm
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 901 lgdlikvtps  skivgdlaqf  mvqnglsrae  aeaqaeelsf  prsvveflqg   yigvphggfp

 961 epfrskvlkd  lprvegrpga  slppldlqal  ekelvdrhge  evtpedvlsa  amypdvfahf

1021 kdftatfgpl  dslntrlflq   gpkiaeefev  elergktlhi  kalavsdlnr  agqrqvffel

1081 ngqlrsilvk  dtqamkemhf  hpkalkdvkg  qigapmpgkv  idikvvagak  vakgqplcvl

1141 samkmetvvt  spmegtvrkv  hvtkdmtleg  ddlileie
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[0085] IO. Eps Domain Containing Protein (RalBP1)

[0086] Eps domain containing protein (RalBP1 protein) has been identified as an Akt substrate that interacts with Akt. Human RalBP1 protein is associated with reference sequence NP_114128 (GenBank Accession No. 13994296). Other relevant sequences include mouse RalBP1 protein associated with reference sequence NP_033074 (GenBank Accession No. 6677715).

NP_114128. RAPBP1 associated Eps domain containing 1 [gi: 13994296]

LOCUS	NP_114128 744 aa linear PRI 05-OCT-2003
DEFINITION	RALBP1 associated Eps domain containing 1; RALBP1 protein [*Homo sapiens*].
ACCESSION	NP_114128
VERSION	NP_114128.1 GI: 13994296
DBSOURCE	REFSEQ: accession NM_031922.1
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 744)
AUTHORS	Xu, J., Zhou, Z., Zeng, L., Huang, Y., Zhao, W., Cheng, C., Xu, M., Xie, Y. and Mao, Y.
TITLE	Cloning, expression and characterization of a novel human REPS1 gene
JOURNAL	Biochim. Biophys. Acta 1522 (2), 118–121 (2001)
MEDLINE	21621408
PUBMED	11750063
COMMENT	PROVISIONAL REFSEQ: This record has not vet been subject to final NCBI review. The reference sequence was derived from AF251052.1.
FEATURES	Location/Qualifiers
source	1 . . . 744 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="6" /map="6q23.1–q24.1"
Protein	1 . . . 744 /product="RALBP1 associated Eps domain containing 1" /note="RALBP1 protein"
variation	97 /allele="V" /allele="G" /db_xref="dbSNP:1212987"
Region	226 . . . 317 /region_name="Eps15 homology domain" /note="EH" /db_xref="CDD:smart00027"
variation	665 /allele="V" /allele="I" /db_xref="dbSNP:1044418"
variation	710 /allele="W" /allele="L" /db_xref="dbSNP:1730376"
CDS	1 . . . 744 /gene="REPS1" /coded by="NM_031922.1:94..2328" /db_xref="GeneID:85021" /db_xref="LocusID:85021"

[0087] Origin

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 61aasyssdsen qgsysgvipp ppgrgqvkkg svshdtvqpr tsadaqepas pvvspqqspp
121tsphtwrkhs rhpsggnser plagpgpfws pfgeaqsgss agdavwsghs ppppqenwvs
181fadtpptstl ltmhpasvqd qttvrtvasa ttaieirrqs ssyddpwkit deqrqyyvnq
241fktiqpdlng fipgsaakef  ftksklpile lshiwelsdf dkdgaltlde fcaafhlvva
301rkngydlpek lpeslmpkli dledsadvgd qpgevgysgs paeappsksp smpslnqtwp
361elnqsseqwe tfserssssq tltqfdsnia padpdtaivh pvpirmtpsk ihmqemelkr
421tgsdhtnpts pllvkpsdll eenkinssvk fasgntvadg ysssdsftsd peqigsnvtr
481qrshsgtspd ntappppppr pqpshsrsss ldmnrtftvt tgqqqagvva hppavpprpq
541psqapgpavh rpvdadglit htstspqqip eqpnfvdfsq fevfaasnvn deqddeaekh
601pevlpaekas dpasslrvak tdskteekta asapanvskg ttplapppkp vrrrlksede
661lrpevdehtq ktgvlaavla sqpsiprsvg kdkkaiqasi rrnketntvl arlnselqqq
721lkdvleeris levqleqlrp fshl
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[0088] IP. Nonmuscle myosin IIA (NMMIIA)

[0089] Nonmuscle myosin IIA (NMMIIA) has been identified as an Akt substrate that interacts with Akt. Human NMMIIA is associated with reference sequence NP_002464 (GenBank Accession No. 12667788). Other relevant sequences include mouse NMMIIA associated with reference sequence NP_071855 (GenBank Accession No. 20137006).

NP_002464. myosin, heavy polypeptide 9, non-muscle [gi: 12667788]

LOCUS	NP_002464 1960 aa linear PRI 06-OCT-2003
DEFINITION	myosin, heavy polypeptide 9, non-muscle [*Homo sapiens*].
ACCESSION	NP_002464
VERSION	NP_002464.1 GI: 12667788
DBSOURCE	REFSEQ: accession NM_002473.2
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 1960)
AUTHORS	Lamant, L., Gascoyne, R. D., Duplantier, M. M., Armstrong, F., Raghab, A., Chhanabhai, M., Rajcan-Separovic, E., Raghab, J., Delsol, G. and Espinos, E.
TITLE	Non-muscle myosin heavy chain (MYH9): a new partner fused to ALK in anaplastic large cell lymphoma
JOURNAL	Genes Chromosomes Cancer 37 (4), 427–432 (2003)
MEDLINE	22683269
PUBMED	12800156
REMARK	GeneRIF: In a case of anaplastic large cell lymphoma, a portion of MYH9 is found to be fused to the ALK gene in a novel chromosomal abnormality, t(2; 22)(p23; q11.2).
REFERENCE	2 (residues 1 to 1960)
AUTHORS	Deutsch, S., Rideau, A., Bochaton-Piallat, M. L., Merla, G., Geinoz, A., Gabbiani, G., Schwede, T., Matthes, T., Antonarakis, S. E. and Beris, P.
TITLE	Asp1424Asn MYH9 mutation results in an unstable protein responsible for the phenotypes in May-Hegglin anomaly/Fechtner syndrome
JOURNAL	Blood 102 (2), 529–534 (2003)
MEDLINE	22718684
PUBMED	12649151
REMARK	GeneRIF: The Asp1424Asn mutation in the MYH9 gene causes the May-Hegglin anomaly, Fechtner syndrome, Sebastian syndrome, & Epstein syndrome, which result from a highly unstable protein & failure to reorganize the megakaryocyte cytoskeleton for platelet production.

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NP_002464. myosin, heavy polypeptide 9, non-muscle [gi: 12667788]

REFERENCE	3 (residues 1 to 1960)
AUTHORS	Seri, M., Pecci, A., Di Bari, F., Cusano, R., Savino, M., Panza, E., Nigro, A., Noris, P., Gangarossa, S., Rocca, B., Gresele, P., Bizzaro, N., Malatesta, P., Koivisto, P. A., Longo, I., Musso, R., Pecoraro, C., Iolascon, A., Magrini, U., Rodriguez Soriano, J., Renieri, A., Ghiggeri, G. M., Ravazzolo, R., Balduini, C. L. and Savoia, A.
TITLE	MYH9-related disease: May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome are not distinct entities but represent a variable expression of a single illness
JOURNAL	Medicine (Baltimore) 82 (3), 203–215 (2003)
MEDLINE	22676762
PUBMED	12792306
REMARK	GeneRIF: MYH9 gene is implicated in May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome and Epstein syndrome which are autosomal dominant macrothrombocytopenias.
REFERENCE	4 (residues 1 to 1960)
	AUTHORS Mhatre, A. N., Kim, Y., Brodie, H. A. and Lalwani, A. K.
TITLE	Macrothrombocytopenia and progressive deafness is due to a mutation in MYH9
JOURNAL	Otol Neurotol 24 (2), 205–209 (2003)
MEDLINE	22508750
PUBMED	12621333
REMARK	GeneRIF: A single base pair transition in MYH9, resulting in an amino acid substitution D1424N, is responsible for macrothrombocytopenia and hearing loss in the kindred under study.
REFERENCE	5 (residues 1 to 1960)
AUTHORS	Ghiggeri, G. M., Caridi, G., Magrini, U., Sessa, A., Savoia, A., Seri, M., Pecci, A., Romagnoli, R., Gangarossa, S., Noris, P., Sartore, S., Necchi, V., Ravazzolo, R. and Balduini, C. L.
TITLE	Genetics, clinical and pathological features of glomerulonephritis associated with mutations of nonmuscle myosin IIA (Fechtner syndrome)
JOURNAL	Am. J. Kidney Dis. 41 (1), 95–104 (2003)
MEDLINE	22386817
PUBMED	12500226
REMARK	GeneRIF: A major role is indicated for the NMMHC-IIA abnormality in the pathogenesis of leukocyte, platelet, and kidney defects in Fechtner syndrome.
REFERENCE	6 (residues 1 to 1960)
AUTHORS	Rey, M., Vicente-Manzanares, M., Viedma, F., Yanez-Mo, M., Urzainqui, A., Barreiro, O., Vazquez, J. and Sanchez-Madrid, F.
TITLE	Cutting edge: association of the motor protein nonmuscle myosin heavy chain-IIA with the C terminus of the chemokine receptor CXCR4 in T lymphocytes
JOURNAL	J. Immunol. 169 (10), 5410–5414 (2002)
MEDLINE	22309087
PUBMED	12421915
REMARK	GeneRIF: Motor protein nonmuscle myosin heavy chain-IIA and CXCR$ colocalize at the leading edge of migrating T lymphocytes, together with filamentous actin and myosin light chain.
REFERENCE	7 (residues 1 to 1960)
AUTHORS	Seri, M., Savino, M., Bordo, D., Cusano, R., Rocca, B., Meloni, I., Di Bari, F., Koivisto, P. A., Bolognesi, M., Ghiggeri, G. M., Landolfi, R., Balduini, C. L., Zelante, L., Ravazzolo, R., Renieri, A. and Savoia, A.
TITLE	Epstein syndrome: another renal disorder with mutations in the nonmuscle myosin heavy chain 9 gene
JOURNAL	Hum. Genet. 110 (2), 182–186 (2002)
MEDLINE	21932559
PUBMED	11935325
REMARK	GeneRIF: mutation in epstein syndrome
REFERENCE	8 (residues 1 to 1960)
AUTHORS	Heath, K. E., Campos-Barros, A., Toren, A., Rozenfeld-Granot, G., Carlsson, L. E., Savige, J., Denison, J. C., Gregory, M. C., White, J. G., Barker, D. F., Greinacher, A., Epstein, C. J., Glucksman, M. J. and Martignetti, J. A.
TITLE	Nonmuscle myosin heavy chain IIA mutations define a spectrum of autosomal dominant macrothrombocytopenias: May-Hegglin anomaly and Fechtner, Sebastian, Epstein, and Alport-like syndromes

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NP_002464. myosin, heavy polypeptide 9, non-muscle [gi: 12667788]

JOURNAL	Am. J. Hum. Genet. 69 (5), 1033–1045 (2001)
MEDLINE	21473756
PUBMED	11590545
REMARK	GeneRIF: mutations cause a spectrum of autosomal dominant macrothrombocytopenias: May-Hegglin anomaly and Fechtner, Sebastian, Epstein, and Alport-like syndromes; hence, the name 'MYHIIA syndrome' is proposed to encompass all of these disorders
REFERENCE	9 (residues 1 to 1960)
AUTHORS	Toothaker, L. E., Gonzalez, D. A., Tung, N., Lemons, R. S., Le Beau, M. M., Arnaout, M. A., Clayton, L. K. and Tenen, D. G.
TITLE	Cellular myosin heavy chain in human leukocytes: isolation of 5' cDNA clones, characterization of the protein, chromosomal localization, and upregulation during myeloid differentiation
JOURNAL	Blood 78 (7), 1826–1833 (1991)
MEDLINE	92003925
PUBMED	1912569
REFERENCE	10 (residues 1 to 1960)
AUTHORS	Simons, M., Wang, M., McBride, O. W., Kawamoto, S., Yamakawa, K., Gdula, D., Adelstein, R. S. and Weir, L.
TITLE	Human nonmuscle myosin heavy chains are encoded by two genes located on different chromosomes
JOURNAL	Circ. Res. 69 (2), 530–539 (1991)
MEDLINE	91316803
PUBMED	1860190
REFERENCE	11 (residues 1 to 1960)
AUTHORS	Saez, C. G., Myers, J. C., Shows, T. B. and Leinwand, L. A.
TITLE	Human nonmuscle myosin heavy chain mRNA: generation of diversity through alternative polyadenylylation
JOURNAL	Proc. Natl. Acad. Sci. U.S.A. 87 (3), 1164–1168 (1990)
MEDLINE	90138958
PUBMED	1967836
REFERENCE	12 (residues 1 to 1960)
AUTHORS	Lee, C. L. and Atassi, M. Z.
TITLE	Enzymic and immunochemical properties of lysozyme. Accurate definition of the antigenic site around the disulphide bridge 30–115 (site 3) by 'surface-simulation' synthesis
JOURNAL	Biochem. J. 167 (3), 571–581 (1977)
MEDLINE	78103135
PUBMED	603622
COMMENT	PROVISIONAL REFSEQ: This record has not yet been subject to final
NCBI	review. The reference sequence was derived from Z82215.1.
FEATURES	Location/Qualifiers
source	1 . . . 1960 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="22" /map="22q13.1"
Protein	1 . . . 1960 /product="myosin, heavy polypeptide 9, non-muscle"
Region	83 . . . 764 /region_name="Myosin head (motor domain)" /note="myosin head" /db_xref="CDD:pfam00063"
Region	1091 . . . 1924 /region_name="Myosin tail. The myosin molecule is a multi-subunit complex made up of two heavy chains and four light chains it is a fundamental contractile protein found in all eukaryote cell types. This family consists of the coiled-coil myosin heavy chain tail region. The coiled-coil is composed of the tail from two molecules of myosin. These can then assemble into the macromolecular thick filament. The coiled-coil region provides the structural backbone the thick filament" /note="Myosin tail" /db_xref="CDD:pfam01576"
variation	1626 /allele="V" /allele="I" /db_xref="dbSNP:2269529"
CDS	1 . . . 1960 /gene="MYH9" /coded_by="NM_002473.2:1..5883" /note="match: proteins: Tr:Q63731 Sw:P35579 Tr:O93522 Tr:Q62812 Sw:P14105 Sw:P10587 Tr:O08638 Sw:P35748

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NP_002464. myosin, heavy polypeptide 9, non-muscle [gi: 12667788]
Tr:O08639 Tr:O94944 Tr:Q02015; go_component: non-muscle myosin [goid 0005860] [evidence TAS] [pmid 1967836]; go_component: kinesin complex [goid 0005871] [evidence IEA]; go_component: myosin [goid 0016459] [evidence IEA]; go_function: adenosinetriphosphatase activity [goid 0004002] [evidence NR] [pmid 1967836]; go_function: motor activity [goid 0003774] [evidence NR]; go_function: actin binding [goid 0003779] [evidence IEA]; go_function: ATP binding [goid 0005524] [evidence IEA]; go_function: calmodulin binding [goid 0005516] [evidence IEA]; go_process: hearing [goid 0007605] [evidence IEA]; go_process: protein amino acid alkylation [goid 0008213] [evidence IEA]" /db_xref="GeneID:4627" /db_xref="LocusID:4627" /db_xref="MIM:160775"

[**0090**] Origin

[SEQ ID NO:27]

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   1 maqqaadkyl yvdknfinnp laqadwaakk lvwvpsdksg fepaslkeev geeaivelve

  61 ngkkvkvnkd diqkmnppkf skvedmaelt clneasvlhn lkeryysgli ytysglfcvv

 121 inpyknlpiy seeivemykg kkrhempphi yaitdtayrs mmqdredqsi lctgesgagk

 181 tentkkviqy layvasshks kkdqgelerq llqanpilea fgnaktvknd nssrfgkfir

 241 infdvngyiv ganietylle ksrairqake ertfhifyyl lsgagehlkt dlllepynky

 301 rflsnghvti pgqqdkdmfq etmeamrimg ipeeeqmgll rvisgvlqlg nivfkkernt

 361 dqasmpdnta aqkvshllgi nvtdftrgil tprikvgrdy vqkaqtkeqa dfaiealaka

 421 tyermfrwlv lrinkaldkt krqgasfigi ldiagfeifd lnsfeqlcin ytneklqqlf

 481 nhtmfileqe eyqregiewn fidfgldlqp cidliekpag ppgilallde ecwfpkatdk

 541 sfvekvmqeq gthpkfqkpk qlkdkadfci ihyagkvdyk adewlmknmd plndniatll

 601 hqssdkfvse lwkdvdriig ldqvagmset alpgafktrk gmfrtvgqly keqlaklmat

 661 lrntnpnfvr ciipnhekka gkldphlvld qlrcngvleg iricrqgfpn rvvfqefrqr

 721 yeiltpnsip kgfmdgkqac vlmikaleld snlyrigqsk vffragvlah leeerdlkit

 781 dviigfqacc rgylarkafa krqqqltamk vlqrncaayl klrnwqwwrl ftkvkpllqv

 841 srqeeemmak eeelvkvrek qlaaenrlte metlqsqlma eklqlqeqlq aetelcaeae

 901 elrarltakk qeleeichdl earveeeeer cqhlqaekkk mqqniqelee qleeeesarq

 961 klqlekvtte aklkkleeeq iiledqnckl akekklledr iaefttnlte eeekskslak

1021 lknkheamit dleerlrree kqrqelektr rklegdstdl sdqiaelqaq iaelkmqlak

1081 keeelqaala rveeeaaqkn malkkirele sqiselqedl eserasrnka ekqkrdlgee

1141 lealkteled tldstaaqqe lrskreqevn ilkktleeea ktheaqiqem rqkhsqavee

1201 laeqleqtkr vkanlekakq tlenergela nevkvllqgk gdsehkrkkv eaqlqelqvk

1261 fnegervrte ladkvtklqv eldnvtglls qsdsksskslt kdfsalesql qdtqellqee

1321 nrqklslstk lkqvedekns freqleeeee akhnlekqia tlhaqvadmk kkmedsvgcl
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1381 etaeevkrkl qkdleglsqr heekvaaydk lektktrlqq elddllvdld hqrqsacnle

1441 kkqkkfdqll aeektisaky aeerdraeae areketkals laraleeame qkaelerlnk

1501 qfrtemedlm sskddvgksv helekskral eqqveemktq leeledelqa tedaklrlev

1561 nlqamkaqfe rdlqgrdeqs eekkkqlvrq vremeaeled erkqrsmava arkklemdlk

1621 dleahidsan knrdeaikql rklqaqmkdc mrelddtras reeilaqake nekklksmea

1681 emiqlqeela aaerakrqaq qerdeladei anssgkgala leekrrlear iaqleeelee

1741 eqgntelind rlkkanlqid qintdlnler shaqknenar qqlerqnkel kvklqemegt

1801 vkskykasit aleakiaqle eqldnetker qaackqvrrt ekklkdvllq vdderrnaeq

1861 ykdqadkast rlkqlkrqle eaeeeaqran asrrklqrel edatetadam nrevsslknk

1921 lrrgdlpfvv prrmarkgag dgsdeevdgk adgaeakpae
```

[0091] IQ. Stress 70 Protein (P66 mot1/GRP75)

[0092] Stress 70 Protein (P66 mot1/GRP75) has been identified as an Akt substrate that interacts with Akt. Human P66 mot1/GRP75 is associated with reference sequence NP_004125 (GenBank Accession No. 24234688). Other relevant sequences include mouse P66 mot1/GRP75 (GenBank Accession No. 6754256).

NP_004125. heat shock 70kDa protein 9B precursor [gi: 24234688]

LOCUS	NP_004125 679 aa linear PRI 05-OCT-2003
DEFINITION	heat shock 70kDa protein 9B precursor; heat shock 70 kD protein 9; stress-70 protein, mitochondrial; 75 kDa glucose regulated protein; peptide-binding protein 74; mortalin, perinuclear; p66-mortalin [*Homo sapiens*].
ACCESSION	NP_004125
VERSION	NP_004125.3 GI: 24234688
DBSOURCE	REFSEQ: accession NM_004134.3
KEYWORDS	.
SOURCE	*Homo sapiens* (human)
ORGANISM	*Homo sapiens* Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; *Homo*.
REFERENCE	1 (residues 1 to 679)
AUTHORS	Kaul, S. C, Yaguchi, T., Taira, K., Reddel, R. R. and Wadhwa, R.
TITLE	Overexpressed mortalin (mot-2)/mthsp70/GRP75 and hTERT cooperate to extend the in vitro lifespan of human fibroblasts
JOURNAL	Exp. Cell Res. 286 (1), 96–101 (2003)
MEDLINE	22615561
PUBMED	12729798
REMARK	GeneRIF: Results demonstrate that mot-2 and telomerase can cooperate in the immortalization process.
REFERENCE	2 (residues 1 to 679)
AUTHORS	Wadhwa, R., Yaguchi, T., Hasan, M. K., Mitsui, Y., Reddel, R. R. and Kaul, S. C.
TITLE	Hsp70 family member, mot-2/mthsp70/GRP75, binds to the cytoplasmic sequestration domain of the p53 protein
JOURNAL	Exp. Cell Res. 274 (2), 246–253 (2002)
MEDLINE	21898287
PUBMED	11900485
REMARK	GeneRIF: Cytoplasmic sequestration and inactivation of p53 by mot-2 occurs by its binding to the cytoplasmic sequestration domain; perturbation of mot-p53 interactions can be employed to abrogate cytoplasmic retention of wild-type p53 in tumors.
REFERENCE	3 (residues 1 to 679)
AUTHORS	Carette, J., Lehnert, S. and Chow, T. Y.
TITLE	Implication of PBP74/mortalin/GRP75 in the radio-adaptive response
JOURNAL	Int. J. Radiat. Biol. 78 (3), 183–190 (2002)
MEDLINE	21859237
PUBMED	11869473
REMARK	GeneRIF: Implication of PBP74/mortalin/GRP75 in the radio-adaptive response.

-continued

NP_004125. heat shock 70kDa protein 9B precursor [gi: 24234688]

REFERENCE	4 (residues 1 to 679)
AUTHORS	Kaul, S. C., Wadhwa, R., Matsuda, Y., Hensler, P. J., Pereira-Smith, O. M., Komatsu, Y. and Mitsui, Y.
TITLE	Mouse and human chromosomal assignments of mortalin, a novel member of the murine hsp70 family of proteins
JOURNAL	FEBS Lett. 361 (2–3), 269–272 (1995)
MEDLINE	95212562
PUBMED	7698336
REFERENCE	5 (residues 1 to 679)
AUTHORS	Bhattacharyya, T., Karnezis, A. N., Murphy, S. P., Hoang, T., Freeman, B. C., Phillips, B. and Morimoto, R. I.
TITLE	Cloning and subcellular localization of human mitochondrial hsp70
JOURNAL	J. Biol. Chem. 270 (4), 1705–1710 (1995)
MEDLINE	95130547
PUBMED	7829505
REFERENCE	6 (residues 1 to 679)
AUTHORS	Domanico, S. Z., DeNagel, D. C., Dahlseid, J. N., Green, J. M. and Pierce, S. K.
TITLE	Cloning of the gene encoding peptide-binding protein 74 shows that it is a new member of the heat shock protein 70 family
JOURNAL	Mol. Cell. Biol. 13 (6), 3598–3610 (1993)
MEDLINE	93268309
PUBMED	7684501
COMMENT	REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from BC024034.1 and AU130219.1. On Oct 22, 2002 this sequence version replaced gi: 21314627. Summary: The product encoded by this gene belongs to the heat shock protein 70 family which contains both heat-inducible and constitutively expressed members. The latter are called heat-shock cognate proteins. This gene encodes a heat-shock cognate protein. This protein plays a role in the control of cell proliferation. It may also act as a chaperone.
FEATURES	Location/Qualifiers
source	1 . . . 679 /organism="*Homo sapiens*" /db_xref="taxon:9606" /chromosome="5" /map="5q31.1"
Protein	1 . . . 679 /product="heat shock 70kDa protein 9B precursor" /note="heat shock 70kD protein 9; stress-70 protein, mitochondrial; 75 kDa glucose regulated protein; peptide-binding protein 74; mortalin, perinuclear; p66-mortalin"
transit_peptide	1 . . . 51 /note="mitochondrial targeting sequence"
mat_peptide	52 . . . 679 /product="heat shock 70kDa protein 9B"
Region	55 . . . 653 /region_name="Hsp70 protein. Hsp70 chaperones help to fold many proteins. Hsp70 assisted folding involves repeated cycles of substrate binding and release. Hsp70 activity is ATP dependent. Hsp70 proteins are made up of two regions: the amino terminus is the ATPase domain and the carboxyl terminus is the substrate binding region" /note="HSP70" /db_xref="CDD:pfam00012"
CDS	1 . . . 679 /gene="HSPA9B" /coded_by="NM_004134.3:94..2133" /note="go_component: cytoplasm [goid 0005737] [evidence E] [pmid 7684501]; go_component: mitochondrion [goid 0005739] [evidence TAS] [pmid 7829505]; go_function: ATP binding [goid 0005524] [evidence IEA]" /db_xref="GeneID:3313" /db_xref="LocusID:3313" /db_xref="MIM:600548"

[0093] Origin

[SEQ ID NO:28]

```
  1misasraaaa rlvgaaasrg ptaarhqdsw nglsheafrl vsrrdyasea ikgavvgidl

 61gttnscvavm egkqakvlen aegarttpsv vaftadgerl vgmpakrqav tnpnntfyat

121krligrrydd pevqkdiknv pfkivrasng dawveahgkl yspsqigafv lmkmketaen

181ylghtaknav itvpayfnds qrqatkdagq isglnvlrvi neptaaalay gldksedkvi

241avydlgggtf disileiqkg vfevkstngd tflggedfdq allrhivkef kretgvdltk

301dnmalqrvre aaekakcels ssvqtdinlp yltmdssgpk hlnmkltraq fegivtdlir

361rtiapcqkam qdaevsksdi gevilvggmt rmpkvqqtvq dlfgrapska vnpdeavaig

421aaiqggvlag dvtdvllldv tplslgietl ggvftklinr nttiptkksq vfstaadgqt

481qveikvcqge remagdnkll gqftligipp aprgvpqiev tfdidangiv hvsakdkgtg

541reqqiviqss gglskddien mvknaekyae edrrkkerve avnmaegiih dtetkmeefk

601dqlpadecnk lkeeiskmre llarkdsetg enirqaassl qqaslklfem aykkmasere

661gsgsssgtgeq kedqkeekq
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[0094] II. Screening Assays:

[0095] According to the invention, the following assays may be used to identify compounds that modulate interaction (e.g., binding) of Akt or bioactive fragments thereof with Akt substrates or bioactive fragments thereof and hence, insulin response modulators. Such insulin response modulators are particularly useful in regulation of phosphatidylinositol 3-kinase, regulation of insulin signaling to GLUT4, regulation of insulin signaling to glycogen synthase kinase, regulation of intracellular GLUT4 trafficking and regulation of intracellular retention of GLUT4. The assays feature identifying modulators of the activity of Akt substrates or bioactive fragments thereof, including, but not limited to, those activities identified in Table 1 and subsections IA-IQ. In certain embodiments, the assays of the present invention feature identifying compounds that modulate the phosphorylation state of Akt substrates.

[0096] The assays of the present invention are used to identify Akt modulators of the activity of Akt or bioactive fragments thereof or Akt substrates or bioactive fragments thereof. The modulators of the present invention are particularly useful in modulating insulin related activities but can also affect non-insulin related activities. In various embodiments, the modulators may affect activities in non-insulin responsive tissues and cells.

[0097] IIA. Cell Free Assays

[0098] In one embodiment, an assay of the present invention is a cell-free assay in which a composition comprising assay reagents (e.g., an Akt substrate polypeptide, Akt polypeptide or biologically active portions thereof), is contacted with a test compound and the ability of the test compound to modulate binding of the Akt substrate polypeptide to the Akt polypeptide (or bioactive fragments thereof) is determined. Binding of the Akt substrate or Akt (or bioactive fragments thereof) can be accomplished, for example, by coupling the polypeptide or fragment with a radioisotope or enzymatic label such that binding of polypeptide reagents can be determined by detecting the labeled compound or polypeptide in a complex. For example, test compounds or polypeptides can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, polypeptides can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

[0099] Determination of binding of reagents can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA). Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo et al. (1995) *Curr. Opin. Struct. Biol.* 5:699-705. As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcore™). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[0100] In a preferred embodiment, the assay includes contacting Akt polypeptide or biologically active portion thereof with an Akt target molecule, e.g., an akt substrate or a bioactive fragment thereof to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the Akt polypeptide, wherein determining the ability of the test compound to interact with the Akt polypeptide comprises determining the ability of the test compound to preferentially bind to Akt or the bioactive portion thereof as compared to the Akt target molecule (e.g., an Akt substrate). In another embodiment, the assay includes contacting the Akt substrate polypeptide or biologically active portion thereof with an Akt substrate target molecule, e.g., Akt or a bioactive fragment thereof to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to modulate binding between the Akt substrate polypeptide and the Akt polypeptide.

[0101] In another embodiment, the assay is a cell-free assay in which a composition comprising an Akt polypeptide and an Akt substrate polypeptide (or bioactive portions thereof) is contacted with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the Akt polypeptide or Akt substrate polypeptide (or biologically active portions thereof) is determined.

[0102] Determining the ability of the test compound to modulate the activity of an Akt or an Akt substrate polypeptide can be accomplished, for example, by determining the ability of the Akt substrate polypeptide to modulate the activity of a downstream binding partner or target molecule by one of the methods described herein for cell-based assays. For example, the catalytic/enzymatic activity of the target molecule on an appropriate downstream substrate can be determined as previously described.

[0103] In yet another embodiment, the cell-free assay involves contacting an Akt substrate polypeptide or biologically active portion thereof with an Akt substrate target molecule that binds the Akt substrate polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound (e.g., Akt) to preferentially modulate the activity of an Akt substrate binding partner or target molecule, as compared to the Akt substrate.

[0104] In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the Akt substrate or Akt (or target molecules) to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. The ability of a test compound to modulate Akt substrate polypeptide activity, Akt polypeptide activity, interaction of an Akt substrate polypeptide with an Akt polypeptide (or target interaction or activity) in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided so as to add a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/Akt substrate fusion proteins, glutathione-S-transferase/Akt fusion proteins, or target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, Mo.) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed Akt polypeptide or Akt substrate polypeptide (or target polypeptide), and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of Akt substrate binding or activity or Akt binding or activity (or target binding or activity) determined using standard techniques.

[0105] Additional exemplary Akt and/or Akt substrate fusion proteins (or target fusion proteins) include, but are not limited to, chitin binding domain (CBD) fusion proteins, hemagglutinin epitope tagged (HA)-fusion proteins, His fusion proteins (e.g., His_6 tagged proteins), FLAG tagged fusion proteins, AU1 tagged proteins, and the like.

[0106] Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either an Akt polypeptide, an Akt substrate polypeptide or target polypeptide can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated Akt polypeptide, Akt substrate polypeptide or target polypeptide can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with Akt polypeptide, Akt substrate polypeptide or target polypeptide but which do not interfere with binding of the Akt substrate polypeptide to Akt polypeptide (or substrate to target binding) can be derivatized to the wells of the plate, and unbound Akt or Akt substrate polypeptide (or target) trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the Akt substrate polypeptide, Akt polypeptide or target polypeptide, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the Akt substrate polypeptide, Akt polypeptide or target polypeptide.

[0107] In one aspect of the invention, the Akt substrate or Akt polypeptides can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Pat. No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J. Biol. Chem.* 268:12046-12054; Bartel et al. (1993) *Biotechniques* 14:920-924; Iwabuchi et al. (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with Akt substrate or Akt ("binding proteins" or "target molecules") and are involved in Akt substrate or Akt activity. Such target molecules are also likely to be involved in the regulation of cellular activities modulated by the Akt substrate polypeptides or Akt polypeptides.

[0108] At least one exemplary two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a first polypeptide (the "bait" polypeptide, e.g., Akt or Akt substrate) is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, in vivo, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein that interacts with the bait polypeptide.

[0109] Another exemplary two-hybrid system, referred to in the art as the CytoTrap™ system, is based in the modular

nature of molecules of the Ras signal transduction cascade. Briefly, the assay features a fusion protein comprising the "bait" protein and Son-of-Sevenless (SOS) and the cDNAs for unidentified proteins (the "prey") in a vector that encodes myristylated target proteins. Expression of an appropriate bait-prey combination results in translocation of SOS to the cell membrane where it activates Ras. Cytoplasmic reconstitution of the Ras signaling pathway allows identification of proteins that interact with the bait protein of interest, for example, an Akt or Akt substrate protein. Additional mammalian two hybrid systems are also known in the art and can be utilized to identify Akt or Akt substrate interacting proteins. Moreover, at least one of the above-described assays can be utilized to identify Akt-interacting domains or regions of the Akt substrate protein or alternativey, to identify Akt substrate-interacting domain or regions of the Akt protein.

[0110] IIB. Cell Based Assays

[0111] In one embodiment, an assay is a cell-based assay in which a cell capable of expressing a Akt substrate polypeptide, or biologically active portion thereof, is contacted with a test compound and the ability of the test compound to modulate the expression of the Akt substrate polypeptide, or biologically active portion thereof, determined. In another embodiment, an assay is a cell-based assay in which a cell which expresses an Akt substrate polypeptide or Akt polypeptide (or biologically active portions thereof) is contacted with a test compound and the ability of the test compound to modulate the activity of the Akt substrate polypeptide or Akt polypeptide (or biologically active portions thereof) determined. The cell, for example, can be of mammalian origin or a yeast cell. The polypeptides, for example, can be expressed heterologously or native to the cell. Determining the ability of the test compound to modulate the activity of an Akt substrate or Akt polypeptide (or biologically active portions thereof) can be accomplished by assaying for any of the activities of an Akt substrate or Akt polypeptide described herein. Determining the ability of the test compound to modulate the activity of an Akt substrate polypeptide or Akt polypeptide (or biologically active portions thereof) can also be accomplished by assaying for the activity of an Akt substrate target molecule. In one embodiment, determining the ability of the test compound to modulate the activity of an Akt substrate polypeptide, or biologically active portion thereof, is accomplished by assaying for the ability to bind Akt or a bioactive portion thereof. In another embodiment, determining the ability of the test compound to modulate the activity of an Akt substrate polypeptide, or biologically active portion thereof, is accomplished by assaying for the activity of Akt (e.g., by assaying for GLUT4 trafficking). In a preferred embodiment, the cell overexpresses the Akt substrate polypeptide, or biologically active portion thereof, and optionally, overexpresses Akt, or biologically active portion thereof. In another preferred embodiment, the cell expresses Akt, or biologically active portion thereof. In yet another preferred example, the cell is contacted with a compound that stimulates an Akt substrate-associated activity or Akt-associated activity (e.g., insulin) and the ability of a test compound to modulate the Akt substrate-associated activity is determined.

[0112] As used herein, the term "bioactive" fragment includes any portion (e.g., a segment of contiguous amino acids) of an Akt substrate or Akt protein sufficient to exhibit or exert at least one Akt substrate- or Akt-associated activity including, for example, the ability to bind to Akt or Akt substrate, respectively. In various embodiments, the Akt may be one of two isoforms, Akt1 or Akt2. In another embodiment, the bioactive peptide is derived from the amino acid sequence of Akt. In another embodiment, the bioactive peptide corresponds to a fragment or domain as set forth in subsections IA-IQ, supra or a smaller bioactive fragment thereof. In another embodiment, the bioactive peptide is derived from an Akt substrate and can include, for example, amino acid residues sufficient to effect enzymatic activity.

[0113] According to the cell-based assays of the present invention, determining the ability of the test compound to modulate the activity of the Akt polypeptide or biologically active portion thereof, can be determined by assaying for any of the native activities of an Akt polypeptide as described herein. Moreover, the activity of Akt, can be determined by assaying for an indirect activity which is coincident to the activity of Akt. For example, the effect of the test compound on the ability of an Akt-expressing cell to uptake glucose in an insulin-dependent manner can be assayed in the presence of the test compound. Furthermore, determining the ability of the test compound to modulate the activity of the Akt and/or Akt substrate polypeptide or biologically active portion thereof, can be determined by assaying for an activity which is not native to the Akt substrate or Akt polypeptide, but for which the cell has been recombinantly engineered. For example, the cell can be engineered to express a target molecule which is a recombinant protein comprising a bioactive portion of Akt operatively linked to a non-Akt polypeptide. It is also intended that in preferred embodiments, the cell-based assays of the present invention comprise a final step of identifying the compound as a modulator of Akt substrate activity or Akt activity.

[0114] III. Assay Reagents

[0115] IIIA. Test Compounds

[0116] The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K. S. (1997) *Anticancer Drug Des.* 12:145).

[0117] Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop et al. (1994) *J. Med. Chem.* 37:1233.

[0118] Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Biotechniques* 13:412-421), or

on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner U.S. Pat. No. 5,223,409), spores (Ladner U.S. Pat. No. '409), plasmids (Cull et al. (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla et al. (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner supra.).

[0119] In a preferred embodiment, the library is a natural product library.

[0120] IIIB. Antibodies, Bioactive Fragments and Fusion Proteins

[0121] Preferred aspects of the invention feature Akt polypeptides, Akt substrate polypeptides and biologically active portions (i.e., bioactive fragments) of Akt polypeptides or Akt substrate polypeptides, including polypeptide fragments suitable for use in making Akt substrate or Akt fusion proteins. In one embodiment, Akt polypeptides or Akt substrate polypeptides can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. Akt polypeptide or Akt substrate polypeptides can be further derived from said isolated polypeptides using standard enzymatic techniques. In another embodiment, Akt substrate polypeptides, Akt polypeptides or bioactive fragments thereof are produced by recombinant DNA techniques. Alternative to recombinant expression, Akt substrate polypeptides, Akt polypeptides or bioactive fragments thereof can be synthesized chemically using standard peptide synthesis techniques.

[0122] Polypeptides of the invention are preferably "isolated" or "purified". The terms "isolated" and "purified" are used interchangeably herein. "Isolated" or "purified" means that the protein or polypeptide is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the polypeptide is derived, substantially free of other protein fragments, for example, non-desired fragments in a digestion mixture, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations in which the polypeptide is separated from other components of the cells from which it is isolated or recombinantly produced. In one embodiment, the language "substantially free of cellular material" includes preparations of polypeptide having less than about 30% (by dry weight) of non-Akt substrate or non-Akt polypeptide (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-Akt substrate or non-Akt polypeptide, still more preferably less than about 10% of non-Akt substrate or non-Akt polypeptide, and most preferably less than about 5% non-Akt substrate or non-Akt polypeptide. When the polypeptide or protein is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the polypeptide preparation. When the polypeptide or protein is produced by, for example, chemical or enzymatic processing from isolated or purified Akt substrate or Akt protein, the preparation is preferably free of enzyme reaction components or chemical reaction components and is free of non-desired Akt substrate or Akt fragments, i.e., the desired polypeptide represents at least 75% (by dry weight) of the preparation, preferably at least 80%, more preferably at least 85%, and even more preferably at least 90%, 95%, 99% or more or the preparation.

[0123] The language "substantially free of chemical precursors or other chemicals" includes preparations of polypeptide in which the polypeptide is separated from chemical precursors or other chemicals which are involved in the synthesis of the polypeptide. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations having less than about 30% (by dry weight) of chemical precursors or reagents, more preferably less than about 20% chemical precursors or reagents, still more preferably less than about 10% chemical precursors or reagents, and most preferably less than about 5% chemical precursors or reagents.

[0124] Bioactive fragments of Akt substrate or Akt include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the Akt substrate protein or the Akt protein, respectively, which include less amino acids than the full length protein, and exhibit at least one biological activity of the full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the full-length protein. A biologically active portion of an Akt substrate or Akt polypeptide can be a polypeptide which is, for example, 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000 or more amino acids in length. In a preferred embodiment, a bioactive portion of an Akt protein comprises a portion comprising an Akt substrate interacting domain. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native Akt substrate or Akt protein. Mutants of Akt and/or Akt substrate can also be utilized as assay reagents, for example, mutants having reduced, enhanced or otherwise altered biological properties identified according to one of the activity assays described herein.

[0125] As defined herein, an Akt polypeptide or Akt substrate polypeptide of the invention includes polypeptides having the amino acid sequences set forth in subsections IA-IQ, infra, as well as homologs an/or orthologues of said polypeptides, i.e. polypeptides having sufficient sequence identity to function in the same manner as the described polypeptides. To determine the percent identity of two amino acid sequences (or of two nucleotide or amino acid sequences), the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the first sequence or second sequence for optimal alignment). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same residue as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions×100), optionally penalizing the score for the number of gaps introduced and/or length of gaps introduced.

[0126] The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In one embodiment,

the alignment generated over a certain portion of the sequence aligned having sufficient identity but not over portions having low degree of identity (i.e., a local alignment). A preferred, non-limiting example of a local alignment algorithm utilized for the comparison of sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-68, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-77. Such an algorithm is incorporated into the BLAST programs (version 2.0) of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-10. BLAST alignments can be generated and percent identity calculated using BLAST protein searches (e.g., the XBLAST program) using Akt substrate, Akt or a portion thereof as a query, score=50, wordlength=3.

[0127] In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the length of the aligned sequences (i.e., a gapped alignment). To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) *Nucleic Acids Research* 25(17):3389-3402. In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the entire length of the sequences aligned (i.e., a global alignment). A preferred, non-limiting example of a mathematical algorithm utilized for the global comparison of sequences is the algorithm of Myers and Miller, *CABIOS* (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[0128] The invention also provides Akt substrates and Akt chimeric or fusion proteins. As used herein, an Akt substrate or Akt "chimeric protein" or "fusion protein" comprises an Akt substrate or Akt polypeptide operatively linked to a non-Akt substrate polypeptide or non-Akt polypeptide, respectively. A "Akt substrate polypeptide" or "Akt polypeptide" refers to a polypeptide having an amino acid sequence corresponding to the Akt substrate or Akt protein, respectively, whereas a "non-Akt substrate polypeptide" or "non-Akt polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein which is not substantially identical to the Akt substrate protein or Akt protein. Within a fusion protein the Akt substrate or Akt polypeptide can correspond to all or a portion of an Akt substrate or Akt protein. In a preferred embodiment, an Akt substrate or Akt fusion protein comprises at least one biologically active portion of an Akt substrate or Akt protein, respectively. In another preferred embodiment, an Akt substrate or Akt fusion protein comprises at least two biologically active portions of an Akt substrate or Akt protein, respectively. In yet another preferred embodiment, a fusion protein can comprise Akt substrate, or a bioactive portion thereof, operatively linked to Akt, or a bioactive portion thereof, such that Akt substrate and Akt, or their respective bioactive portions are brought into close proximity. Within the fusion protein, the term "operatively linked" is intended to indicate that the Akt substrate or Akt polypeptide and the non-Akt substrate polypeptide or non-Akt polypeptide are fused in-frame to each other. The non-Akt substrate polypeptide or non-Akt polypeptide can be fused to the N-terminus or C-terminus of the Akt substrate polypeptide or Akt polypeptide, respectively.

[0129] For example, in one embodiment, the fusion protein is a GST-fusion protein in which the Akt substrate or Akt sequences are fused to the C-terminus of the GST sequences. In another embodiment, the fusion protein is a chitin binding domain (CBD) fusion protein in which the Akt substrate or Akt sequences are fused to the N-terminus of chitin binding domain (CBD) sequences. Such fusion proteins can facilitate the purification of recombinant Akt substrate or Akt.

[0130] Preferably, a chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology,* eds. Ausubel et al. John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety. An Akt substrate- or Akt-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the Akt substrate or Akt polypeptide.

[0131] An Akt substrate polypeptide or Akt polypeptide, or a portion or fragment of Akt substrate or Akt, can also be used as an immunogen to generate antibodies that bind Akt substrate or Akt or that block Akt substrate/Akt binding using standard techniques for polyclonal and monoclonal antibody preparation. A full-length polypeptide can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. Preferably, an antigenic fragment comprises at least 8 amino acid residues of the amino acid sequence of an Akt substrate or Akt and encompasses an epitope of Akt substrate or Akt such that an antibody raised against the peptide forms a specific immune complex with Akt substrate or Akt, respectively. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of Akt substrate or Akt that are located on the surface of the protein, e.g., hydrophilic regions. Antigenic determinants at the termini of Akt substrate are preferred for the development of antibodies that do not interfere with the Akt substrate:Akt interaction. Alternatively, interfering antibodies can be generated towards antigenic determinants located within the Akt interacting domain of Akt substrate. The latter are preferred for therapeutic purposes.

[0132] An Akt substrate or Akt immunogen typically is used to prepare antibodies by immunizing a suitable subject, (e.g., rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed Akt substrate or Akt polypeptide or a chemically synthesized Akt substrate or

Akt polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic Akt substrate or Akt preparation induces a polyclonal anti-Akt substrate or anti-Akt antibody response, respectively.

[0133] Accordingly, another aspect of the invention pertains to anti-Akt substrate or anti-Akt antibodies. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as Akt substrate or Akt. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind Akt substrate. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of Akt substrate or Akt. A monoclonal antibody composition thus typically displays a single binding affinity for a particular Akt substrate or Akt polypeptide with which it immunoreacts.

[0134] Polyclonal anti-Akt substrate or anti-Akt antibodies can be prepared as described above by immunizing a suitable subject with an Akt substrate or Akt immunogen, respectively. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized Akt substrate or Akt. If desired, the antibody molecules can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the anti-Akt substrate or anti-Akt antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown et al. (1981) *J. Immunol.* 127:539-46; Brown et al. (1980) *J. Biol. Chem* 255:4980-83; Yeh et al. (1976) *PNAS* 76:2927-31; and Yeh et al. (1982) *Int. J. Cancer* 29:269-75), the more recent human B cell hybridoma technique (Kozbor et al. (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985), *Monoclonal Antibodies and Cancer Therapy,* Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally R. H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses,* Plenum Publishing Corp., New York, N.Y. (1980); E. A. Lemer (1981) *Yale J. Biol. Med.,* 54:387-402; M. L. Gefter et al. (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an Akt substrate or Akt immunogen as described above, and the culture supematants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds Akt substrate or Akt, respectively.

[0135] Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-Akt substrate monoclonal antibody (see, e.g., G. Galfre et al. (1977) *Nature* 266:55052; Gefter et al. *Somatic Cell Genet.*, cited supra; Lemer, *Yale J. Biol. Med.,* cited supra; Kenneth, *Monoclonal Antibodies,* cited supra). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (e.g., a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, e.g., the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind Akt substrate or Akt, e.g., using a standard ELISA assay.

[0136] Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-Akt substrate or anti-Akt antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with Akt substrate or Akt to thereby isolate immunoglobulin library members that bind Akt substrate or Akt, respectively. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System,* Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner et al. U.S. Pat. No. 5,223,409; Kang et al. PCT International Publication No. WO 92/18619; Dower et al. PCT International Publication No. WO 91/17271; Winter et al. PCT International Publication WO 92/20791; Markland et al. PCT International Publication No. WO 92/15679; Breitling et al. PCT International Publication WO 93/01288; McCafferty et al. PCT International Publication No. WO 92/01047; Garrard et al. PCT International Publication No. WO 92/09690; Ladner et al. PCT International Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J* 12:725-734; Hawkins et al. (1992) *J. Mol. Biol.* 226:889-896; Clarkson et al. (1991) *Nature* 352:624-628; Gram et al. (1992) *PNAS* 89:3576-3580; Garrad et al. (1991) *Bio/Technology* 9:1373-1377; Hoogenboom et al. (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas et al. (1991) *PNAS* 88:7978-7982; and McCafferty et al. *Nature* (1990) 348:552-554.

[0137] An anti-Akt substrate or anti-Akt antibody (e.g., monoclonal antibody) can be used to isolate Akt substrate or Akt, bioactive portions thereof, or fusion proteins by stan-

dard techniques, such as affinity chromatography or immunoprecipitation. Anti-Akt antibodies or anti-Akt substrate antibodies made according to any of the above-described techniques can be used to detect protein levels in donor or acceptor fractions as part of certain assay methodologies described herein. Detection can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{13}I, ^{35}S or ^{3}H.

[0138] IIIC. Recombinant Expression Vectors and Assay Cells

[0139] Another aspect of the invention pertains to vectors, preferably expression vectors, for producing the proteins reagents of the instant invention. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. A preferred vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector.

[0140] The recombinant expression vectors of the invention comprise a nucleic acid that encodes, for example substrate or Akt or a bioactive fragment or Akt substrate or bioactive fragment, in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to includes promoters, enhancers and other expression control elements (e.g., polyadenylation signals). The expression vectors can be introduced into host cells to thereby produce proteins, including fusion proteins or peptides. Alternatively, retroviral expression vectors and/or adenoviral expression vectors can be utilized to express the proteins of the present invention.

[0141] The recombinant expression vectors of the invention can be designed for expression of Akt substrate or Akt polypeptides in prokaryotic or eukaryotic cells. For example, Akt substrate or Akt polypeptides can be expressed in bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, Calif. (1990).

[0142] Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Purified fusion proteins are particularly useful in the cell-free assay methodologies of the present invention.

[0143] In yet another embodiment, a substrate or Akt-encoding or Akt-substrate-encoding nucleic acid is expressed in mammalian cells, for example, for use in the cell-based assays described herein. When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid).

[0144] Another aspect of the invention pertains to assay cells into which a recombinant expression vector has been introduced. An assay cell can be prokaryotic or eukaryotic, but preferably is eukaryotic. A preferred assay cell is an adipocyte or muscle, for example, a human adipocyte cell, a human muscle cell, an adipocyte cell line (e.g., murine 3T3-L1 cells), or a muscle cell line (e.g., murine C2 or C2C12 cells or rat C6 cells). Human adipocytes can be derived from human adipose tissue as undifferentiated cells and expanded ex vivo prior to differentiation for use in the assays of the present invention. Cell lines are cultured according to art-recognized techniques. Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (*Molecular Cloning: A Laboratory Manual.* 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals. An assay cell of the invention, can be contacted with a test compound and assayed for any Akt substrate and/or Akt biological activity in order to identify the compound as an insulin responsive modulator. Biological activities that can further be assayed as part of the methodologies of the present invention include, but are not limited to, (1) modulation of cellular protein degradation; (2) modulation of fat metabolism; (3) modulation of insulin clearance; (4) modulation of proteosome activation; (5) modulation of ubiquitination; and (6) peroxisome targeting activity. Biological activities that can also be assayed as part of the methodologies of the present invention include, but are not limited to, (1) interaction between Akt substrate or a bioactive fragment thereof with Akt or a bioactive fragment thereof; (2) modulation of vesicle translocation; (3) modulation of GLUT4 transloca-

tion; (4) regulation of intracellular trafficking; (5) regulation of glucose uptake; and (6) regulation of phosphatidylinositol 3-kinase pathway components; and/or regulation of insulin signaling. In addition, other biological activities which may be assayed for include those listed in Table 1 and/or subsections IA-IQ, supra.

[0145] IV. Pharmaceutical Compositions

[0146] This invention further pertains to insulin response modulators identified by the above-described screening assays. Insulin response modulators identified by the above-described screening assays can be tested in an appropriate animal model. For example, an insulin response modulator identified as described herein can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such a modulator. Alternatively, a modulator identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of insulin response modulators identified by the above-described screening assays for therapeutic treatments as described infra.

[0147] Accordingly, the insulin response modulators of the present invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, antibody, or modulatory compound and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0148] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0149] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0150] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0151] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0152] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0153] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transder-

mal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0154] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0155] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0156] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0157] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0158] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0159] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0160] V. Methods of Treatment

[0161] The present invention also features methods of treatment or therapeutic methods. In one embodiment, the invention features a method of treating a subject (e.g., a human subject in need thereof) with a modulatory compound identified according to the present invention, such that a desired therapeutic effect is achieved. In another embodiment, the method involves administering to an isolated tissue or cell line from the subject a modulatory compound identified according to the methodology described herein, such that a desired therapeutic effect is achieved. In a preferred embodiment, the invention features a method of treating a subject having an insulin response disorder, for example, reduced insulin sensitivity or insulin resistance or diabetes (e.g., Type II diabetes). The present invention also provides for therapeutic methods of treating a subject having pre-diabetes or symptoms thereof, hyperglycemia and/or Type I diabetes. Desired therapeutic effects include a modulation of any Akt substrate-, Akt- or Akt substrate/Akt-associated activity, as described herein. A preferred therapeutic effect is modulation of glucose uptake and/or transport. Desired therapeutic effects also include, but are not limited to curing or healing the subject, alleviating, relieving, altering or ameliorating a disease or disorder in the subject or at least one symptom of said disease or disorder in the subject, or otherwise improving or affecting the health of the subject. A preferred aspect of the invention pertains to methods of modulating Akt substrate/Akt interactions for therapeutic purposes.

[0162] The modulators identified by the methods disclosed herein may be used in a subject to modulate insulin responsiveness, regulate glucose transport, regulate gluconeogenesis, regulate glucose homeostasis, and to regulate blood glucose levels.

[0163] The effectiveness of treatment of a subject with an insulin response modulator can be accomplished by (i) detecting the level of insulin responsiveness or, alternatively, glucose tolerance in the subject prior to treating with an appropriate modulator; (ii) detecting the level of insulin responsiveness or, alternatively, glucose tolerance in the subject prior post treatment with the modulator; (iii) comparing the levels pre-administration and post administration; and (iv) altering the administration of the modulator to the subject accordingly. For example, increased administration of the modulator may be desirable if the subject continues to demonstrate insensitive insulin responsiveness.

[0164] Alternatively, the effectiveness of treatment of a subject with an insulin response modulator can be accom-

plished by (i) detecting the blood glucose or glucose tolerance in the subject prior to treating with an appropriate modulator; (ii) detecting the blood glucose level or, alternatively, glucose tolerance in the subject prior post treatment with the modulator; (iii) comparing the levels pre-administration and post administration; and (iv) altering the administration of the modulator to the subject accordingly. For example, increased or sustained administration of the modulator may be desirable if the subject fails to adequately clear blood glucose.

[0165] VI. Diagnostic Assays

[0166] The present invention is based at least in part on the discovery that the Akt substrates identified above and Akt interact and are proposed to be involved in regulating insulin responsiveness in a subject. Based on the proposed role for Akt substrate:Akt in normal insulin responsiveness, aberrant Akt substrate:Akt interaction, expression and/or activity may be associated with abnormal insulin responsiveness. Accordingly, the present invention also features diagnostic assays, for determining aberrant Akt substrate:Akt interaction, expression or activity, in the context of a biological sample (e.g., blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder (e.g., abnormal insulin responsiveness), or is at risk of developing such a disorder. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing such a disorder (e.g., a disorder associated with aberrant Akt substrate expression or activity). Such assays can be used for prognostic or predictive purpose to thereby phophylactically treat an individual prior to the onset of a disease or disorder. A preferred agent for detecting an Akt substrate or Akt protein is an antibody capable of binding to substrate or Akt, respectively, preferably an antibody with a detectable label. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. The invention also encompasses kits for the detection of aberrant Akt substrate:Akt interaction, expression or activity in a biological sample. For example, the kit can comprise a labeled compound or agent capable of detecting Akt substrate and/or Akt in a biological sample; means for determining the amount of Akt substrate and/or Akt in the sample; and/or means for comparing the amount of Akt substrate in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit.

[0167] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXEMPLIFICATION

EXAMPLE 1

Insulin Signaling Through Akt/Protein Kinase B Analyzed by Small Interfering RNA Mediated Gene Silencing

[0168] In order to determine the importance of Akt1 and Akt2, the following experiment seeks to selectively inhibit the expression of Akt protein kinases in intact cultured adipocytes through the use of interference RNA. This powerful approach overcomes the problems encountered in mouse gene knockouts where loss of both Akt1 and Akt2 genes is lethal. First discovered in *Caenorhabditis elegans* (Fire et al. (1998) *Nature* 391:806-811), this gene-silencing technique uses double-stranded RNA to activate nuclease-containing protein complexes (RNA-induced silencing complex) to target a specific MRNA species, which is then degraded (Hammond et al. (2001) *Nature* 404:293-296; Hammond et al. (2001) *Science* 293:1146-1150). Before insertion into protein-silencing complexes, processing of double-stranded RNA into small interfering RNA (siRNA) duplexes of 21-23 nt occurs by enzymes known as Dicers (Bernstein et al. (2001) *Nature* 409:363-366; Zamore et al. (2000) *Cell* 101:25-33; Elbashir et al. (2000) *Genes Dev.* 15:188-200). Extension of the technique to mammalian cells has involved the use of synthetic siRNA duplexes of 21-base lengths transfected directly into cultured cells, where decreased levels of selected proteins can be observed in response to siRNA after 24-72 h (Elbashir et al. (2001) *Nature* 411:494-498). The following example demonstrates the details of a method that can be used successfully to silence genes in insulin-sensitive cultured adipocytes and to show that virtual complete ablation of Akt1 and ≈70% depletion of Akt2 can be achieved. Combined depletion of these Akt isoforms largely attenuates insulin signaling to both GLUT4 glucose transporters and glycogen synthase kinase (GSK)-3, demonstrating an obligatory role of Akt protein kinases in these insulin-signaling cascades.

[0169] Materials and Methods

[0170] Materials. Human insulin was obtained from Eli Lilly (Indianapolis, Ind.). Goat polyclonal anti-Akt1 Ab (antigen human Akt1 peptide near C terminus, sc-7126), horseradish peroxidase-conjugated donkey anti-goat IgG, mouse monoclonal anti-lamin A/C (sc7293), monoclonal anti-GSK-3α/β, and polyclonal anti-protein kinase C (PKC)λ/ξ (C-20, sc216) were from Santa Cruz Biotechnology (Santa Cruz, Calif.). Rabbit polyclonal anti-Akt2 Ab (antigen peptide at C-terminal of human Akt2) was provided by the University of Pennsylvania (Philadelphia, Pa.). Rabbit polyclonal Ab against adipocyte complement-related protein of 30 kDa (Acrp30) was from Affinity BioReagents (Golden, Colo.) and Ab against nonmuscle myosin IIB was from Covance (Richmond, Calif.). Polyclonal Abs against phospho-Akt Thr-308/309, phospho-GSK-α/β (Ser-21/9), and phospho-Erk-1/2 were from Cell Signaling Technology (Beverly, Mass.). Monoclonal phosphotyrosine Ab (4G10) was from Upstate USA (Charlottesville, Va.). The FITC-conjugated goat anti-mouse was from BioSource International (Camarillo, Calif.). The plasmid expressing Myc-tagged GLUT4-EGFP was constructed as described in Jiang et al. (2002) *J. Biol. Chem.* 277:509-515.

[0171] Design and Synthesis of siRNA Duplexes. The 21-mer sense and antisense strands of RNA oligonucleotides were designed as described in Elbashir et al. (2001) *Nature* 411:494-498. The RNA oligonucleotides were synthesized in the 2'-ACE(™) protected form, which enhances overall RNA stability and resistance to nucleases. The complementary sense and antisense strands of RNA oligonucleotides were mixed, 2'-deprotected, annealed, and purified by PAGE. Gel-purified duplexes were subsequently desalted by using reverse-phase column chromatography, followed by

washing with 75% ethanol twice to ensure complete salt removal and dried by use of a Speed-Vac. The pellets were resuspended in nuclease-free water before transfection into cultured cells.

[0172] Cell Culture and Electroporation of 3T3L1 Adipocytes. The 3T3-L1 fibroblasts were grown in DMEM supplemented with 10% FBS, 50 μg/ml streptomycin, and 50 units/ml penicillin and differentiated into adipocytes as described in Harrison et al., (1990) *J. Biol. Chem* 265:20106-20116. The 3T3-L1 adipocytes were transfected with siRNA duplexes by electroporation. In brief, the adipocytes at day 5 of differentiation were detached from culture dishes with 0.25% trypsin and 0.5 mg of collagenase/ml in PBS, washed twice, and resuspended in PBS. Approximately 5 million cells (half of the cells from one p150 dish) were then mixed with siRNA duplexes, which were delivered to the cells by a pulse of electroporation with a Bio-Rad gene pulser II system (Bio-Rad Laboratories, Hercules, Calif.) at the setting of 0.18 kV and 960 μF capacitance. After electroporation, cells were immediately mixed with fresh medium for 10 min before reseeding onto multiple-well plates designed for the deoxyglucose uptake assay, Western blotting, and immunofluorescence microscopic analysis.

[0173] Immunofluorescence Microscopy. To visualize lamin A/C, cells were fixed with 4% formaldehyde and permeabilized with PBS containing 1% FBS and 0.5% Triton X-100. Cells were then incubated with primary mouse anti-rat lamin A/C Ab for overnight at 4° C. After washing, cells were incubated with FITC-labeled goat anti-mouse IgG for 30 min at room temperature. To analyze GLUT4 translocation in adipocytes, cells were cotransfected with Myc-GLUT4-EGFP plasmid and siRNAs by electroporation. After this, adipocytes were serum-starved, treated as noted in the figure legends, washed, and immunostained by using the procedure as described in Jiang et al. (2002), *J. Biol. Chem.* 277:509-515. In brief, the cell surface Myc-GLUT4-EGFP was visualized with mouse anti-Myc Ab and rhodamine-labeled anti-mouse secondary Ab. After washing, the coverslips were mounted in 90% glycerol containing 2.5% diazabicyclo[2.2.2]octane. Fluorescence microscopy was carried out with a IX70-inverted microscope (Olympus, Melville, N.Y.) with charge-coupled device camera (Roper Scientific, Trenton, N.J.) and METAMORPH image processing software (Universal Imaging, Downington, Pa.).

[0174] Western Blotting. After experimental treatments, the cells were solubilized as described in Jiang et al. (2002), *J. Biol. Chem.* 277:509-515. To detect phosphorylation of Akt Thr-308/309, GSK-3α/β Ser-21/9, and tyrosine phosphorylation of Erk-1/2, 50 μg protein from 3T3-L1 adipocyte lysates were resolved with 8% SDS/PAGE and electrotransferred to nitrocellulose membranes, which were incubated with anti-phospho-specific Abs (1:1,000 dilution) overnight at 4° C. and then with horseradish peroxidase-linked anti-rabbit IgG Abs (1:10,000 dilution) for 1 h at room temperature. Tyrosin phosphorylation of insulin receptor substrate (IRS) proteins was detected with monoclonal phosphotyrosine Ab followed by horseradish peroxidase-linked anti-mouse IgG Abs. Akt1 was detected with primary goat polyclonal Ab (1:750 dilution) and secondary horseradish peroxidase-linked donkey anti-goat Ab (1:10,000 dilution). Primary rabbit polyclonal Abs against Akt2 (1:1,000 dilution), nonmuscle myosin IIB (0.1 μg/ml), Acrp30 (0.5 μg/ml), and PKCλ/ξ (1:500 dilution) were used to detect their antigens by using 25 μg of protein from total cell lysates. The membranes were washed with wash buffer (PBS, pH 7.4/0.1% Tween 20) for 1 h at room temperature after incubation with each Ab. Finally, the levels of target proteins or phosphorylated proteins were detected with an enhanced chemiluminescence kit. To use the same nitrocellulose membrane to detect several proteins and phosphoproteins, the blots were incubated with gentle shaking in stripping buffer (62.5 mM Tris-HCl, pH 6.7/100 mM 2-mercaptoethanol/2% SDS) for 30-45 min at 60° C. and washed for at least 1 h with wash buffer before reblotting with the Ab designed for the next experiment.

[0175] The 2-Deoxyglucose Uptake Assay. Insulin-stimulated glucose transport in 3T3-L1 adipocytes was estimated by measuring 2-deoxyglucose uptake. In brief, siRNA-transfected cells were reseeded on 12-well plates and cultured for 40 h and then washed twice with DMEM before incubation with DMEM containing 0.5% BSA for 4 h at 37° C. Cells were then washed twice with Krebs-Ringer's Hepes buffer (130 mM NaCl/5 mM KCl/1.3 mM $CaCl_2$/1.3 mM $MgSO_4$/25 mM Hepes, pH 7.4) and further starved for 1.5 h with Krebs-Ringer's Hepes buffer supplemented with 0.5% BSA and 2 mM sodium pyruvate. Cells were then stimulated with insulin for 30 min at 37° C. Glucose uptake was initiated by addition of [1,2-^{3}H]2-deoxy-D-glucose to a final assay concentration of 100 μM for 5 min at 37° C. Assays were terminated by four washes with ice-cold Krebs-Ringer's Hepes buffer, and the cells were solubilized with 0.4 ml of 1% Triton X-100, and ^{3}H was determined by scintillation counting. Nonspecific deoxyglucose uptake was measured in the presence of 20 μM cytochalasin B and subtracted from each determination to obtain specific uptake.

[0176] Results and Discussion

[0177] siRNA-Induced Gene Silencing in Cultured Adipocytes. To test whether siRNA can induce gene-specific silencing in adipocytes, the gene encoding lamin A/C, previously shown to be sensitive to this technique in other cells, was first targeted. Cy3-tagged 21-nt siRNA duplexes directed against mouse lamin A/C mRNA were designed and synthesized (**FIG. 1A**). The initial experiments showed that conditions developed for siRNA-mediated gene silencing in other cells types (Elbashir et al. (2001) *Nature* 411:494-498) worked well in 3T3-L1 fibroblasts (**FIG. 1B** Right), but failed to work in 3T3-L1 adipocytes (not shown). Consequently, an alternate methodology was developed to transfect lamin A/C siRNA into 3T3-L1 adipocytes by using electroporation. With this method, Cy3-siRNA was introduced with virtually 100% efficiency into the cultured adipocytes, and by 48 h nearly all cells showed loss of nuclear lamin A/C compared to cells transfected with a scrambled Cy3-tagged siRNA species (**FIG. 1B**). Quantification of these results showed that adding 20 nmol of siRNA to a suspension of 5×10^6 adipocytes results in loss of lamin A/C in ≈90% of the adipocytes with no detectable toxicity (**FIG. 1C**). These findings provide the basis for reliable gene silencing in insulin-sensitive cultured adipocytes.

[0178] Two siRNA species directed against each of the Akt isoforms Akt1 and Akt2 were then tested for their abilities to inhibit expression of these protein kinases in 3T3-L1 adipocytes (**FIG. 2**). Each of the Akt1-directed

siRNA species inhibited expression of Akt1 protein at both 24 and 48 h after transfection. One of these (akt1b) directed virtually total ablation of Akt1 expression by 48 h, whereas Akt2 expression was unaffected (**FIGS. 2B and 3A** and B). Similarly, Akt2 expression could be selectively attenuated by ≈70% after transfection of the siRNA species akt2b, whereas the akt2a siRNA was less effective (**FIGS. 2B and 3A** and B). Interestingly, the akt1b and akt2b siRNA species that show most efficacy are targeted to similar regions of the Akt1 and Akt2 mRNA sequences that encode amino acids 351-357 and 352-358 in Akt1 and Akt2, respectively (**FIG. 2A**). Whether the secondary structure of this Akt mRNA region is particularly susceptible to siRNA-directed RNA degradation requires further study. The selectivity of akt1b vs. akt2b siRNAs to silence their respective target mRNA species is apparent even though only 4 of 21 nucleotides are different (**FIG. 2A**). Expression of several other unrelated proteins (e.g., myosin IIB shown in **FIGS. 2, 3** and **5** and adipocyte-specific protein Acrp30 shown in **FIGS. 3 and 5**) were also unaffected by akt1b or akt2b siRNAs.

[**0179**] Differential Effects of Akt1 and Akt2 Gene Silencing on Insulin Signaling. Akt1 and Akt2 are phosphorylated and activated by the protein kinase PDK1 at Thr-308 or Thr-309, respectively, in the activation T-loop, and further activation occurs through phosphorylatian at Ser-473 or Ser-474, respectively (Alessi et al. (1997) *Curr. Biol.* 7:776-789; Williams et al. (2000) *Curr. Biol.* 10:439-448; Brazil et al. (2001) *Trends Biochem. Sci.* 26:657-664). The effects of selective loss of Akt1 vs. Akt2 proteins on insulin-stimulated phosphorylation of total Thr-308/309 contained in both proteins were assessed by Western blotting with an anti-phospho-Thr-308/309 Ab. Total loss of Akt1 protein resulted in only a 10-20% reduction in total Thr-308/309 phosphorylation of Akt protein kinases in cultured 3T3-L1 adipocytes, consistent with previous results showing Akt1 is much less abundant than Akt2 in adipocytes (Hill et al. (1999) *Mol. Cell. Biol.* 19:7771-7781; Summers et al. (1999) *J. Biol. Chem.* 274: 23858-23867; Calera et al. (1998) *J. Biol. Chem.* 273:7201-7204). In contrast, reduction of Akt2 expression by ≈70% caused a marked 55-60% decrease in insulin-stimulated Thr phosphorylation of the Akt protein kinases (**FIG. 3**). Taken together, these data confirm the predominance of Akt2 over Akt1 in insulin-sensitive cultured adipocytes (Hill et al. (1999) *Mol. Cell. Biol.* 19:7771-7781).

[**0180**] Next, the consequences of the selective attenuation of Akt1 or Akt2 expression on a downstream target of insulin signaling-GSK-3 were assessed (Cross et al. (1995) *Nature* 378:785-789; Cohen et al. (2001) *Nat. Rev. Mol. Cell Biol.* 2:769-776). GSK-3α is phosphorylated by Akt protein kinases in response to the hormone in a dose-dependent manner (**FIG. 4**). In three independent experiments, loss of 95% or more of Akt1 directed by the akt1b siRNA caused no significant attenuation of insulin-mediated GSK-3α phosphorylation (**FIGS. 4A** and B), although a 10-20% effect may go undetected in these studies. In contrast, attenuation of Akt2 expression by 70% caused ≈40% inhibition of insulin-mediated GSK-3α phosphorylation (**FIGS. 4A** and B and **5A** and C). In control studies, no diminution of insulin signaling to the mitogen-activated protein kinases Erk-1 and Erk-2 was observed when either Akt1 or Akt2 are depleted (**FIGS. 4C** and D), confirming the specificity of the effect of silencing the Akt protein kinases by this method. These data indicate that insulin action on GSR-3α in cultured adipocytes specifically requires Akt2.

[**0181**] Redundancy of Akt1 and Akt2 in Insulin Signaling. Applying this same approach to hexose transport regulation, ablation of Akt1 expression (**FIG. 5A**) leads to a small but significant 20-30% decrease in insulin-stimulated 2-deoxyglucose uptake in 3T3-L1 adipocytes (**FIG. 5A**). Akt2 protein depletion to ≈70% of normal levels dampened the insulin response by 50-58%. These data indicate that both Akt1 and Akt2 contribute to insulin responsiveness of hexose transport in cultured adipocytes roughly in proportion to their contributions to total activated Akt in these cells (see Hill et al. (1999) *Mol. Cell. Biol.* 19: 7771-7781 and **FIG. 3**). Subsequently, the effects of depleting both Akt1 and Akt2 in 3T3-L1 adipocytes were tested by using the combination of akt1b and akt2b siRNA species (**FIGS. 5A** and C). This combined treatment virtually completely ablated Akt1 expression and reduced Akt2 expression by ≈65% whereas insulin-stimulated phosphorylation of total Akt detected by anti-phospho Thr-308/309 Ab decreased by 81% (**FIG. 5A**). Importantly, insulin-stimulated deoxyglucose uptake was inhibited by nearly 80% under these conditions, compared to ≈58% when only Akt2 was depleted (**FIG. 5C**). Under these conditions, GLUT4 expression was unchanged (not shown). In control experiments to test whether engagement of the gene silencing process itself nonspecifically inhibits insulin signaling, no significant effect of lamin siRNA on insulin-stimulated glucose transport were observed under conditions where lamin A/C protein levels were markedly reduced (**FIG. 1** and data not shown). Taken together, these data demonstrate that although Akt2 is the major protein kinase required in this response, Akt1 can also play a role. Thus under conditions where insulin-stimulated glucose uptake is significantly compromised by partial depletion of Akt2, Akt1 is required for half of the remaining insulin signal (**FIG. 5C**). GSK-3α phosphorylation in response to insulin was also inhibited to a greater extent when both protein kinases were depleted versus when only Akt2 was reduced (**FIGS. 5A** and C).

[**0182**] In additional control experiments, we tested whether expression of other insulin-signaling elements such as IRS proteins (Li et al. (1999) *J. Biol. Chem.* 274:9351-9356) or PKCλ/ξ (Kotani et al. (1998) *Mol. Cell. Biol.* 18:6971-6982; Standaert et al. (1997) *J. Biol. Chem.* 272:30075-30082) is affected by Akt1 or Akt2 siRNAs. As shown in **FIG. 5A**, depletion of Akt1 or Akt2 had no significant effect on insulin-stimulated tyrosine phosphorylation of IRS proteins or expression levels of PKCλ/ξ.

[**0183**] The effect of combined depletion of both Akt1 and Akt2 by siRNA on insulin-mediated GLUT4 translocation was next examined in 3T3-L1 adipocytes. Cotransfection of myc-GLUT4-EGFP plasmid DNA with the mixture of akt1b and akt2b siRNAs was performed, and 48 h later reductions of ≈90% and 65% of Akt1 and Akt2 protein levels, respectively, were observed (**FIG. 6B**). This combined knockdown of Akt1 and Akt2 proteins resulted in the loss of insulin-stimulated cell surface Myc signal (detected by anti-Myc Ab) in ≈70% of adipocytes transfected with the Myc-GLUT4-GFP construct (**FIGS. 6A** and C). Quantifying the ratio of cell surface Myc rim signal over the total Myc-GLUT4-GFP signal in positive transfected cells revealed that loss of both Akt1 and Akt2 resulted in a 60% decrease in insulin-stimulated Myc-GLUT4-GFP on the cell surface (**FIG. 6D**). The attenuation of GLUT4 responsiveness is observed at both maximal and submaximal concentrations of

insulin (**FIG. 6C**), whereas no significant effect of Akt depletion on GLUT4 translocation in the absence of insulin is detected.

[**0184**] The findings presented here show an absolute requirement of Akt protein kinases for normal insulin signaling to glucose transport and GSK-3α and imply direct proportionality of total available Akt1 plus Akt2 to the degree of insulin responsiveness (**FIG. 5**). This conclusion is in keeping with the similar insulin dose-response relationships observed for activation of total Akt and glucose transport (compare **FIGS. 3C and 5B**). Progressive loss of Akt1, Akt2, or both leads to a correspondingly progressive loss in glucose transport stimulation (**FIG. 5**). These considerations show that Akt1 can in part replace Akt2 to sustain glucose transport responsiveness, potentially providing an explanation for why skeletal muscle of $Akt2^{-/-}$ mice exhibits only a mild impairment in insulin responsiveness (Cho et al. (2001) *Science* 292:1728-1731). No data on insulin signaling in muscle or fat cells from $Akt1^{-/-}$ mice have been published, but the normal glucose tolerance in these animals (Cho et al. (2001) *J. Biol. Chem.* 276:38349-38352) is consistent with our data (**FIG. 5**) that Akt2 alone can sustain most of the insulin-regulated glucose uptake. Although it is possible that other signaling pathways and protein kinases are also involved in insulin action on glucose transport, the results underscore the absolute requirement of Akt for this process.

EXAMPLE 2

Identification And Characterization of Akt Substrates

[**0185**] The present invention relates to the fields of diabetes and insulin resistance. Insulin response modulating compounds (e.g., insulin response stimulatory compounds) will permit restoration of insulin sensitivity and result in lower blood glucose levels. Insulin resistance results from the inability of normally insulin-responsive tissues to respond to the hormone. In normally functioning muscle and fat cells, insulin binds to its receptor on the surface of the cell and initiates a series of intracellular events including the transport of glucose into the cell. This glucose transport is the key event that regulates the level of glucose in the blood and maintains normoglycemia. The inability to take up glucose into these cells is a condition called insulin resistance and is often found in the diabetic or pre-diabetic state. The activity and regulation of the molecules regulating glucose transport in the cell have been widely studied in the hopes that understanding their function may lead to the ability to alter that function and restore responsiveness to insulin. The insulin-responsive glucose transporter, GLUT4, is found in intracellular vesicles that are located in an insulin-sensitive intracellular compartment. In the absence of insulin, these GLUT4-containing vesicles (G4Vs) are retained in the cytosol of the cell. Upon insulin binding to its receptor at the surface of the cell the G4Vs move from this compartment to the cell surface where GLUT4 is then at the cell surface and can transport glucose into the cell. One protein that has been shown to be involved in such trafficking and the associated insulin signaling pathway is Akt. To further identify substrates involved in the trafficking and regulation of GLUT4 and, more generally, the insulin mediated response of a cell, a biochemical screen was set up to identify proteins from insulin responsive cells that interact with Akt.

[**0186**] Anti-Akt substrate antibody was generated, expressed in and purified from *E. coli* and used as an affinity reagent to bind proteins that interact with Akt. The antibody was specific for phosphorylated sites on Akt substrates. The antibody was exposed to a adipocyte cell extract. The tagged phosphorylated proteins were immunoprecipitated by techniques well known in the art. The resulting precipitated proteins were characterized through mass spectrometry. Table 1 identifies the proteins identified according to the described methodology.

[**0187**] Equivalents

[**0188**] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

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         35                  40                  45

Thr Met Ala Leu Tyr Asn Pro Ile Pro Val Arg Gln Asn Cys Phe Thr
     50                  55                  60

Val Asn Arg Ser Leu Phe Ile Phe Gly Glu Asp Asn Ile Val Arg Lys
 65                  70                  75                  80

Tyr Ala Lys Lys Leu Ile Asp Trp Pro Pro Phe Glu Tyr Met Ile Leu
                 85                  90                  95

Ala Thr Ile Ile Ala Asn Cys Ile Val Leu Ala Leu Glu Gln His Leu
            100                 105                 110

Pro Glu Asp Asp Lys Thr Pro Met Ser Arg Arg Leu Glu Lys Thr Glu
        115                 120                 125

Pro Tyr Phe Ile Gly Ile Phe Cys Phe Glu Ala Gly Ile Lys Ile Val
    130                 135                 140

Ala Leu Gly Phe Ile Phe His Lys Gly Ser Tyr Leu Arg Asn Gly Trp
145                 150                 155                 160

Asn Val Met Asp Phe Ile Val Val Leu Ser Gly Ile Leu Ala Thr Ala
                165                 170                 175

Gly Thr His Phe Asn Thr His Val Asp Leu Arg Thr Leu Arg Ala Val
            180                 185                 190

Arg Val Leu Arg Pro Leu Lys Leu Val Ser Gly Ile Pro Ser Leu Gln
        195                 200                 205

Ile Val Leu Lys Ser Ile Met Lys Ala Met Val Pro Leu Leu Gln Ile
    210                 215                 220

Gly Leu Leu Leu Phe Phe Ala Ile Leu Met Phe Ala Ile Ile Gly Leu
225                 230                 235                 240

Glu Phe Tyr Ser Gly Lys Leu His Arg Ala Cys Phe Met Asn Asn Ser
                245                 250                 255

Gly Ile Leu Glu Gly Phe Asp Pro Pro His Pro Cys Gly Val Gln Gly
            260                 265                 270

Cys Pro Ala Gly Tyr Glu Cys Lys Asp Trp Ile Gly Pro Asn Asp Gly
        275                 280                 285

Ile Thr Gln Phe Asp Asn Ile Leu Phe Ala Val Leu Thr Val Phe Gln
    290                 295                 300

Cys Ile Thr Met Glu Gly Trp Thr Thr Val Leu Tyr Asn Thr Asn Asp
305                 310                 315                 320

Ala Leu Gly Ala Thr Trp Asn Trp Leu Tyr Phe Ile Pro Leu Ile Ile
                325                 330                 335

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385                 390                 395                 400

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                405                 410                 415

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Ser Ala Lys Val Asp Gly Val Ser Tyr Phe Arg His Lys Glu Arg Leu
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465                 470                 475                 480

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                485                 490                 495

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            500                 505                 510

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        515                 520                 525

Gly Met Gly Pro Arg Leu Tyr Phe His Ser Ser Phe Asn Cys Phe Asp
    530                 535                 540

Phe Gly Val Thr Val Gly Ser Ile Phe Glu Val Val Trp Ala Ile Phe
545                 550                 555                 560

Arg Pro Gly Thr Ser Phe Gly Ile Ser Val Leu Arg Ala Leu Arg Leu
                565                 570                 575

Leu Arg Ile Phe Lys Ile Thr Lys Tyr Trp Ala Ser Leu Arg Asn Leu
            580                 585                 590

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        595                 600                 605

Leu Leu Phe Leu Phe Ile Val Val Phe Ala Leu Leu Gly Met Gln Leu
    610                 615                 620

Phe Gly Gly Arg Phe Asn Phe Asn Asp Gly Thr Pro Ser Ala Asn Phe
625                 630                 635                 640

Asp Thr Phe Pro Ala Ala Ile Met Thr Val Phe Gln Ile Leu Thr Gly
                645                 650                 655

Glu Asp Trp Asn Glu Val Met Tyr Asn Gly Ile Arg Ser Gln Gly Gly
            660                 665                 670

Val Ser Ser Gly Met Trp Ser Ala Ile Tyr Phe Ile Val Leu Thr Leu
        675                 680                 685

Phe Gly Asn Tyr Thr Leu Leu Asn Val Phe Leu Ala Ile Ala Val Asp
    690                 695                 700

Asn Leu Ala Asn Ala Gln Glu Leu Thr Lys Asp Glu Gln Glu Glu Glu
705                 710                 715                 720

Glu Ala Phe Asn Gln Lys His Ala Leu Gln Lys Ala Lys Glu Val Ser
                725                 730                 735

Pro Met Ser Ala Pro Asn Met Pro Ser Ile Glu Arg Glu Arg Arg Arg
            740                 745                 750

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Leu Asn Ala His Pro Ser Leu Tyr Arg Arg Pro Arg Ala Ile Glu Gly
                805                 810                 815

Leu Ala Leu Gly Leu Ala Leu Glu Lys Phe Glu Glu Glu Arg Ile Ser
            820                 825                 830

Arg Gly Gly Ser Leu Lys Gly Asp Gly Gly Asp Arg Ser Ser Ala Leu
        835                 840                 845

Asp Asn Gln Arg Thr Pro Leu Ser Leu Gly Gln Arg Glu Pro Pro Trp
    850                 855                 860

Leu Ala Arg Pro Cys His Gly Asn Cys Asp Pro Thr Gln Gln Glu Ala
865                 870                 875                 880

Gly Gly Gly Glu Ala Val Val Thr Phe Glu Asp Arg Ala Arg His Arg
                885                 890                 895

Gln Ser Gln Arg Arg Ser Arg His Arg Arg Val Arg Thr Glu Gly Lys
            900                 905                 910

Glu Ser Ser Ser Ala Ser Arg Ser Arg Ser Ala Ser Gln Glu Arg Ser
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Leu Asp Glu Ala Met Pro Thr Glu Gly Glu Lys Asp His Glu Leu Arg
    930                 935                 940

Gly Asn His Gly Ala Lys Glu Pro Thr Ile Gln Glu Glu Arg Ala Gln
945                 950                 955                 960

Asp Leu Arg Arg Thr Asn Ser Leu Met Val Ser Arg Gly Ser Gly Leu
                965                 970                 975

Ala Gly Gly Leu Asp Glu Ala Asp Thr Pro Leu Val Leu Pro His Pro
            980                 985                 990

Glu Leu Glu Val Gly Lys His Val Val Leu Thr Glu Gln Glu Pro Glu
        995                1000                1005

Gly Ser Ser Glu Gln Ala Leu Leu Gly Asn Val Gln Leu Asp Met Gly
   1010                1015                1020

Arg Val Ile Ser Gln Ser Glu Pro Asp Leu Ser Cys Ile Thr Ala Asn
1025                1030                1035                1040

Thr Asp Lys Ala Thr Thr Glu Ser Thr Ser Val Thr Val Ala Ile Pro
               1045                1050                1055

Asp Val Asp Pro Leu Val Asp Ser Thr Val Val His Ile Ser Asn Lys
           1060                1065                1070

Thr Asp Gly Glu Ala Ser Pro Leu Lys Glu Ala Glu Ile Arg Glu Asp
       1075                1080                1085

Glu Glu Glu Val Glu Lys Lys Lys Gln Lys Lys Glu Lys Arg Glu Thr
   1090                1095                1100

Gly Lys Ala Met Val Pro His Ser Ser Met Phe Ile Phe Ser Thr Thr
1105                1110                1115                1120

Asn Pro Ile Arg Arg Ala Cys His Tyr Ile Val Asn Leu Arg Tyr Phe
               1125                1130                1135

Glu Met Cys Ile Leu Leu Val Ile Ala Ala Ser Ser Ile Ala Leu Ala
           1140                1145                1150

Ala Glu Asp Pro Val Leu Thr Asn Ser Glu Arg Asn Lys Val Leu Arg
       1155                1160                1165
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Tyr Phe Asp Tyr Val Phe Thr Gly Val Phe Thr Phe Glu Met Val Ile
   1170               1175               1180

Lys Met Ile Asp Gln Gly Leu Ile Leu Gln Asp Gly Ser Tyr Phe Arg
1185               1190               1195               1200

Asp Leu Trp Asn Ile Leu Asp Phe Val Val Val Val Gly Ala Leu Val
               1205               1210               1215

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

Lys Thr Ile Lys Ser Leu Arg Val Leu Arg Val Leu Arg Pro Leu Lys
       1235               1240               1245

Thr Ile Lys Arg Leu Pro Lys Leu Lys Ala Val Phe Asp Cys Val Val
   1250               1255               1260

Thr Ser Leu Lys Asn Val Phe Asn Ile Leu Ile Val Tyr Lys Leu Phe
1265               1270               1275               1280

Met Phe Ile Phe Ala Val Ile Ala Val Gln Leu Phe Lys Gly Lys Phe
               1285               1290               1295

Phe Tyr Cys Thr Asp Ser Ser Lys Asp Thr Glu Lys Glu Cys Ile Gly
           1300               1305               1310

Asn Tyr Val Asp His Glu Lys Asn Lys Met Glu Val Lys Gly Arg Glu
       1315               1320               1325

Trp Lys Arg His Glu Phe His Tyr Asp Asn Ile Ile Trp Ala Leu Leu
   1330               1335               1340

Thr Leu Phe Thr Val Ser Thr Gly Glu Gly Trp Pro Gln Val Leu Gln
1345               1350               1355               1360

His Ser Val Asp Val Thr Glu Glu Asp Arg Gly Pro Ser Arg Ser Asn
               1365               1370               1375

Arg Met Glu Met Ser Ile Phe Tyr Val Val Tyr Phe Val Val Phe Pro
           1380               1385               1390

Phe Phe Phe Val Asn Ile Phe Val Ala Leu Ile Ile Ile Thr Phe Gln
       1395               1400               1405

Glu Gln Gly Asp Lys Met Met Glu Glu Cys Ser Leu Glu Lys Asn Glu
   1410               1415               1420

Arg Ala Cys Ile Asp Phe Ala Ile Ser Ala Lys Pro Leu Thr Arg Tyr
1425               1430               1435               1440

Met Pro Gln Asn Arg His Thr Phe Gln Tyr Arg Val Trp His Phe Val
               1445               1450               1455

Val Ser Pro Ser Phe Glu Tyr Thr Ile Met Ala Met Ile Ala Leu Asn
           1460               1465               1470

Thr Val Val Leu Met Met Lys Tyr Tyr Ser Ala Pro Cys Thr Tyr Glu
       1475               1480               1485

Leu Ala Leu Lys Tyr Leu Asn Ile Ala Phe Thr Met Val Phe Ser Leu
   1490               1495               1500

Glu Cys Val Leu Lys Val Ile Ala Phe Gly Phe Leu Asn Tyr Phe Arg
1505               1510               1515               1520

Asp Thr Trp Asn Ile Phe Asp Phe Ile Thr Val Ile Gly Ser Ile Thr
               1525               1530               1535

Glu Ile Ile Leu Thr Asp Ser Lys Leu Val Asn Thr Ser Gly Phe Asn
           1540               1545               1550

Met Ser Phe Leu Lys Leu Phe Arg Ala Ala Arg Leu Ile Lys Leu Leu
       1555               1560               1565

Arg Gln Gly Tyr Thr Ile Arg Ile Leu Leu Trp Thr Phe Val Gln Ser
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   1570                1575                1580

Phe Lys Ala Leu Pro Tyr Val Cys Leu Leu Ile Ala Met Leu Phe Phe
1585                1590                1595                1600

Ile Tyr Ala Ile Ile Gly Met Gln Val Phe Gly Asn Ile Lys Leu Asp
               1605                1610                1615

Glu Glu Ser His Ile Asn Arg His Asn Asn Phe Arg Ser Phe Phe Gly
           1620                1625                1630

Ser Leu Met Leu Leu Phe Arg Ser Ala Thr Gly Glu Ala Trp Gln Glu
       1635                1640                1645

Ile Met Leu Ser Cys Leu Gly Glu Lys Gly Cys Glu Pro Asp Thr Thr
   1650                1655                1660

Ala Pro Ser Gly Gln Asn Glu Asn Glu Arg Cys Gly Thr Asp Leu Ala
1665                1670                1675                1680

Tyr Val Tyr Phe Val Ser Phe Ile Phe Phe Cys Ser Phe Leu Met Leu
               1685                1690                1695

Asn Leu Phe Val Ala Val Ile Met Asp Asn Phe Glu Tyr Leu Thr Arg
           1700                1705                1710

Asp Ser Ser Ile Leu Gly Pro His His Leu Asp Glu Phe Val Arg Val
       1715                1720                1725

Trp Ala Glu Tyr Asp Arg Ala Ala Cys Gly Arg Ile His Tyr Thr Glu
   1730                1735                1740

Met Tyr Glu Met Leu Thr Leu Met Ser Pro Pro Leu Gly Leu Gly Lys
1745                1750                1755                1760

Arg Cys Pro Ser Lys Val Ala Tyr Lys Arg Leu Val Leu Met Asn Met
               1765                1770                1775

Pro Val Ala Glu Asp Met Thr Val His Phe Thr Ser Thr Leu Met Ala
           1780                1785                1790

Leu Ile Arg Thr Ala Leu Asp Ile Lys Ile Ala Lys Gly Gly Ala Asp
       1795                1800                1805

Arg Gln Gln Leu Asp Ser Glu Leu Gln Lys Glu Thr Leu Ala Ile Trp
   1810                1815                1820

Pro His Leu Ser Gln Lys Met Leu Asp Leu Leu Val Pro Met Pro Lys
1825                1830                1835                1840

Ala Ser Asp Leu Thr Val Gly Lys Ile Tyr Ala Ala Met Met Ile Met
               1845                1850                1855

Asp Tyr Tyr Lys Gln Ser Lys Val Lys Lys Gln Arg Gln Gln Leu Glu
           1860                1865                1870

Glu Gln Lys Asn Ala Pro Met Phe Gln Arg Met Glu Pro Ser Ser Leu
       1875                1880                1885

Pro Gln Glu Ile Ile Ala Asn Ala Lys Ala Leu Pro Tyr Leu Gln Gln
   1890                1895                1900

Asp Pro Val Ser Gly Leu Ser Gly Arg Ser Gly Tyr Pro Ser Met Ser
1905                1910                1915                1920

Pro Leu Ser Pro Gln Asp Ile Phe Gln Leu Ala Cys Met Asp Pro Ala
               1925                1930                1935

Asp Asp Gly Gln Phe Gln Glu Arg Gln Ser Leu Val Val Thr Asp Pro
           1940                1945                1950

Ser Ser Met Arg Arg Ser Phe Ser Thr Ile Arg Asp Lys Arg Ser Asn
       1955                1960                1965

Ser Ser Trp Leu Glu Glu Phe Ser Met Glu Arg Ser Ser Glu Asn Thr
   1970                1975                1980
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Tyr Lys Ser Arg Arg Arg Ser Tyr His Ser Ser Leu Arg Leu Ser Ala
1985              1990                1995                2000

His Arg Leu Asn Ser Asp Ser Gly His Lys Ser Asp Thr His Pro Ser
              2005                2010                2015

Gly Gly Arg Glu Arg Arg Arg Ser Lys Glu Arg Lys His Leu Leu Ser
          2020                2025                2030

Pro Asp Val Ser Arg Cys Asn Ser Glu Glu Arg Gly Thr Gln Ala Asp
      2035                2040                2045

Trp Glu Ser Pro Glu Arg Arg Gln Ser Arg Ser Pro Ser Glu Gly Arg
  2050                2055                2060

Ser Gln Thr Pro Asn Arg Gln Gly Thr Gly Ser Leu Ser Glu Ser Ser
2065              2070                2075                2080

Ile Pro Ser Val Ser Asp Thr Ser Thr Pro Arg Arg Ser Arg Arg Gln
              2085                2090                2095

Leu Pro Pro Val Pro Pro Lys Pro Arg Pro Leu Leu Ser Tyr Ser Ser
          2100                2105                2110

Leu Ile Arg His Ala Gly Ser Ile Ser Pro Pro Ala Asp Gly Ser Glu
      2115                2120                2125

Glu Gly Ser Pro Leu Thr Ser Gln Ala Leu Glu Ser Asn Asn Ala Trp
  2130                2135                2140

Leu Thr Glu Ser Ser Asn Ser Pro His Pro Gln Gln Arg Gln His Ala
2145              2150                2155                2160

Ser Pro Gln Arg Tyr Ile Ser Glu Pro Tyr Leu Ala Leu His Glu Asp
              2165                2170                2175

Ser His Ala Ser Asp Cys Val Glu Glu Glu Thr Leu Thr Phe Glu Ala
          2180                2185                2190

Ala Val Ala Thr Ser Leu Gly Arg Ser Asn Thr Ile Gly Ser Ala Pro
      2195                2200                2205

Pro Leu Arg His Ser Trp Gln Met Pro Asn Gly His Tyr Arg Arg Arg
  2210                2215                2220

Arg Arg Gly Gly Pro Gly Pro Gly Met Met Cys Gly Ala Val Asn Asn
2225              2230                2235                2240

Leu Leu Ser Asp Thr Glu Glu Asp Asp Lys Cys
              2245                2250


<210> SEQ ID NO 8
<211> LENGTH: 2382
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Ser Gly Gly Ala Ala Glu Lys Gln Ser Ser Thr Pro Gly Ser Leu
  1               5                  10                  15

Phe Leu Ser Pro Pro Ala Pro Ala Pro Lys Asn Gly Ser Ser Ser Asp
             20                  25                  30

Ser Ser Val Gly Glu Lys Leu Gly Ala Ala Ala Ala Asp Ala Val Thr
         35                  40                  45

Gly Arg Thr Glu Glu Tyr Arg Arg Arg Arg His Thr Met Asp Lys Asp
     50                  55                  60

Ser Arg Gly Ala Ala Ala Thr Thr Thr Thr Thr Glu His Arg Phe Phe
 65                  70                  75                  80

Arg Arg Ser Val Ile Cys Asp Ser Asn Ala Thr Ala Leu Glu Leu Pro
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                85                  90                  95

Gly Leu Pro Leu Ser Leu Pro Gln Pro Ser Ile Pro Ala Ala Val Pro
            100                 105                 110

Gln Ser Ala Pro Pro Glu Pro His Arg Glu Glu Thr Val Thr Ala Thr
        115                 120                 125

Ala Thr Ser Gln Val Ala Gln Gln Pro Pro Ala Ala Ala Ala Pro Gly
    130                 135                 140

Glu Gln Ala Val Ala Gly Pro Ala Pro Ser Thr Val Pro Ser Ser Thr
145                 150                 155                 160

Ser Lys Asp Arg Pro Val Ser Gln Pro Ser Leu Val Gly Ser Lys Glu
                165                 170                 175

Glu Pro Pro Pro Ala Arg Ser Gly Ser Gly Gly Gly Ser Ala Lys Glu
            180                 185                 190

Pro Gln Glu Glu Arg Ser Gln Gln Gln Asp Asp Ile Glu Glu Leu Glu
        195                 200                 205

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

Ile Glu Ile Gly Arg Gly Ser Phe Lys Thr Val Tyr Lys Gly Leu Asp
225                 230                 235                 240

Thr Glu Thr Thr Val Glu Val Ala Trp Cys Glu Leu Gln Asp Arg Lys
                245                 250                 255

Leu Thr Lys Ser Glu Arg Gln Arg Phe Lys Glu Glu Ala Glu Met Leu
            260                 265                 270

Lys Gly Leu Gln His Pro Asn Ile Val Arg Phe Tyr Asp Ser Trp Glu
        275                 280                 285

Ser Thr Val Lys Gly Lys Lys Cys Ile Val Leu Val Thr Glu Leu Met
    290                 295                 300

Thr Ser Gly Thr Leu Lys Thr Tyr Leu Lys Arg Phe Lys Val Met Lys
305                 310                 315                 320

Ile Lys Val Leu Arg Ser Trp Cys Arg Gln Ile Leu Lys Gly Leu Gln
                325                 330                 335

Phe Leu His Thr Arg Thr Pro Pro Ile Ile His Arg Asp Leu Lys Cys
            340                 345                 350

Asp Asn Ile Phe Ile Thr Gly Pro Thr Gly Ser Val Lys Ile Gly Asp
        355                 360                 365

Leu Gly Leu Ala Thr Leu Lys Arg Ala Ser Phe Ala Lys Ser Val Ile
    370                 375                 380

Gly Thr Pro Glu Phe Met Ala Pro Glu Met Tyr Glu Glu Lys Tyr Asp
385                 390                 395                 400

Glu Ser Val Asp Val Tyr Ala Phe Gly Met Cys Met Leu Glu Met Ala
                405                 410                 415

Thr Ser Glu Tyr Pro Tyr Ser Glu Cys Gln Asn Ala Ala Gln Ile Tyr
            420                 425                 430

Arg Arg Val Thr Ser Gly Val Lys Pro Ala Ser Phe Asp Lys Val Ala
        435                 440                 445

Ile Pro Glu Val Lys Glu Ile Ile Glu Gly Cys Ile Arg Gln Asn Lys
    450                 455                 460

Asp Glu Arg Tyr Ser Ile Lys Asp Leu Leu Asn His Ala Phe Phe Gln
465                 470                 475                 480

Glu Glu Thr Gly Val Arg Val Glu Leu Ala Glu Glu Asp Asp Gly Glu
                485                 490                 495
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Lys Ile Ala Ile Lys Leu Trp Leu Arg Ile Glu Asp Ile Lys Lys Leu
            500                 505                 510

Lys Gly Lys Tyr Lys Asp Asn Glu Ala Ile Glu Phe Ser Phe Asp Leu
        515                 520                 525

Glu Arg Asp Val Pro Glu Asp Val Ala Gln Glu Met Val Glu Ser Gly
    530                 535                 540

Tyr Val Cys Glu Gly Asp His Lys Thr Met Ala Lys Ala Ile Lys Asp
545                 550                 555                 560

Arg Val Ser Leu Ile Lys Arg Lys Arg Glu Gln Arg Gln Leu Val Arg
                565                 570                 575

Glu Glu Gln Glu Lys Lys Lys Gln Glu Glu Ser Ser Leu Lys Gln Gln
            580                 585                 590

Val Glu Gln Ser Ser Ala Ser Gln Thr Gly Ile Lys Gln Leu Pro Ser
        595                 600                 605

Ala Ser Thr Gly Ile Pro Thr Ala Ser Thr Thr Ser Ala Ser Val Ser
    610                 615                 620

Thr Gln Val Glu Pro Glu Glu Pro Glu Ala Asp Gln His Gln Gln Leu
625                 630                 635                 640

Gln Tyr Gln Gln Pro Ser Ile Ser Val Leu Ser Asp Gly Thr Val Asp
                645                 650                 655

Ser Gly Gln Gly Ser Ser Val Phe Thr Glu Ser Arg Val Ser Ser Gln
            660                 665                 670

Gln Thr Val Ser Tyr Gly Ser Gln His Glu Gln Ala His Ser Thr Gly
        675                 680                 685

Thr Val Pro Gly His Ile Pro Ser Thr Val Gln Ala Gln Ser Gln Pro
    690                 695                 700

His Gly Val Tyr Pro Pro Ser Ser Val Ala Gln Gly Gln Ser Gln Gly
705                 710                 715                 720

Gln Pro Ser Ser Ser Ser Leu Thr Gly Val Ser Ser Ser Gln Pro Ile
                725                 730                 735

Gln His Pro Gln Gln Gln Gln Gly Ile Gln Gln Thr Ala Pro Pro Gln
            740                 745                 750

Gln Thr Val Gln Tyr Ser Leu Ser Gln Thr Ser Thr Ser Ser Glu Ala
        755                 760                 765

Thr Thr Ala Gln Pro Val Ser Gln Pro Gln Ala Pro Gln Val Leu Pro
    770                 775                 780

Gln Val Ser Ala Gly Lys Gln Leu Pro Val Ser Gln Pro Val Pro Thr
785                 790                 795                 800

Ile Gln Gly Glu Pro Gln Ile Pro Val Ala Thr Gln Pro Ser Val Val
                805                 810                 815

Pro Val His Ser Gly Ala His Phe Leu Pro Val Gly Gln Pro Leu Pro
            820                 825                 830

Thr Pro Leu Leu Pro Gln Tyr Pro Val Ser Gln Ile Pro Ile Ser Thr
        835                 840                 845

Pro His Val Ser Thr Ala Gln Thr Gly Phe Ser Ser Leu Pro Ile Thr
    850                 855                 860

Met Ala Ala Gly Ile Thr Gln Pro Leu Leu Thr Leu Ala Ser Ser Ala
865                 870                 875                 880

Thr Thr Ala Ala Ile Pro Gly Val Ser Thr Val Val Pro Ser Gln Leu
                885                 890                 895
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Pro Thr Leu Leu Gln Pro Val Thr Gln Leu Pro Ser Gln Val His Pro
            900                 905                 910

Gln Leu Leu Gln Pro Ala Val Gln Ser Met Gly Ile Pro Ala Asn Leu
        915                 920                 925

Gly Gln Ala Ala Glu Val Pro Leu Ser Ser Gly Asp Val Leu Tyr Gln
    930                 935                 940

Gly Phe Pro Pro Arg Leu Pro Pro Gln Tyr Pro Gly Asp Ser Asn Ile
945                 950                 955                 960

Ala Pro Ser Ser Asn Val Ala Ser Val Cys Ile His Ser Thr Val Leu
                965                 970                 975

Ser Pro Pro Met Pro Thr Glu Val Leu Ala Thr Pro Gly Tyr Phe Pro
            980                 985                 990

Thr Val Val Gln Pro Tyr Val Glu Ser Asn Leu Leu Val Pro Met Gly
        995                1000                1005

Gly Val Gly Gly Gln Val Gln Val Ser Gln Pro Gly Gly Ser Leu Ala
   1010                1015                1020

Gln Ala Pro Thr Thr Ser Ser Gln Gln Ala Val Leu Glu Ser Thr Gln
1025                1030                1035                1040

Gly Val Ser Gln Val Ala Pro Ala Glu Pro Val Ala Val Ala Gln Pro
                1045                1050                1055

Gln Ala Thr Gln Pro Thr Thr Leu Ala Ser Ser Val Asp Ser Ala His
            1060                1065                1070

Ser Asp Val Ala Ser Gly Met Ser Asp Gly Asn Glu Asn Val Pro Ser
        1075                1080                1085

Ser Ser Gly Arg His Glu Gly Arg Thr Thr Lys Arg His Tyr Arg Lys
   1090                1095                1100

Ser Val Arg Ser Arg Ser Arg His Glu Lys Thr Ser Arg Pro Lys Leu
1105                1110                1115                1120

Arg Ile Leu Asn Val Ser Asn Lys Gly Asp Arg Val Val Glu Cys Gln
                1125                1130                1135

Leu Glu Thr His Asn Arg Lys Met Val Thr Phe Lys Phe Asp Leu Asp
            1140                1145                1150

Gly Asp Asn Pro Glu Glu Ile Ala Thr Ile Met Val Asn Asn Asp Phe
        1155                1160                1165

Ile Leu Ala Ile Glu Arg Glu Ser Phe Val Asp Gln Val Arg Glu Ile
   1170                1175                1180

Ile Glu Lys Ala Asp Glu Met Leu Ser Glu Asp Val Ser Val Glu Pro
1185                1190                1195                1200

Glu Gly Asp Gln Gly Leu Glu Ser Leu Gln Gly Lys Asp Asp Tyr Gly
                1205                1210                1215

Phe Ser Gly Ser Gln Lys Leu Glu Gly Glu Phe Lys Gln Pro Ile Pro
            1220                1225                1230

Ala Ser Ser Met Pro Gln Gln Ile Gly Ile Pro Thr Ser Ser Leu Thr
        1235                1240                1245

Gln Val Val His Ser Ala Gly Arg Arg Phe Ile Val Ser Pro Val Pro
   1250                1255                1260

Glu Ser Arg Leu Arg Glu Ser Lys Val Phe Pro Ser Glu Ile Thr Asp
1265                1270                1275                1280

Thr Val Ala Ala Ser Thr Ala Gln Ser Pro Gly Met Asn Leu Ser His
                1285                1290                1295

Ser Ala Ser Ser Leu Ser Leu Gln Gln Ala Phe Ser Glu Leu Arg Arg
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          1300                1305                1310

Ala Gln Met Thr Glu Gly Pro Asn Thr Ala Pro Pro Asn Phe Ser His
       1315                1320                1325

Thr Gly Pro Thr Phe Pro Val Val Pro Pro Phe Leu Ser Ser Ile Ala
   1330                1335                1340

Gly Val Pro Thr Thr Ala Ala Ala Thr Ala Pro Val Pro Ala Thr Ser
1345                1350                1355                1360

Ser Pro Pro Asn Asp Ile Ser Thr Ser Val Ile Gln Ser Glu Val Thr
              1365                1370                1375

Val Pro Thr Glu Glu Gly Ile Ala Gly Val Ala Thr Ser Thr Gly Val
          1380                1385                1390

Val Thr Ser Gly Gly Leu Pro Ile Pro Pro Val Ser Glu Ser Pro Val
       1395                1400                1405

Leu Ser Ser Val Val Ser Ser Ile Thr Ile Pro Ala Val Val Ser Ile
   1410                1415                1420

Ser Thr Thr Ser Pro Ser Leu Gln Val Pro Thr Ser Thr Ser Glu Ile
1425                1430                1435                1440

Val Val Ser Ser Thr Ala Leu Tyr Pro Ser Val Thr Val Ser Ala Thr
              1445                1450                1455

Ser Ala Ser Ala Gly Gly Ser Thr Ala Thr Pro Gly Pro Lys Pro Pro
          1460                1465                1470

Ala Val Val Ser Gln Gln Ala Ala Gly Ser Thr Thr Val Gly Ala Thr
       1475                1480                1485

Leu Thr Ser Val Ser Thr Thr Thr Ser Phe Pro Ser Thr Ala Ser Gln
   1490                1495                1500

Leu Ser Ile Gln Leu Ser Ser Ser Thr Ser Thr Pro Thr Leu Ala Glu
1505                1510                1515                1520

Thr Val Val Val Ser Ala His Ser Leu Asp Lys Thr Ser His Ser Ser
              1525                1530                1535

Thr Thr Gly Leu Ala Phe Ser Leu Ser Ala Pro Ser Ser Ser Ser Ser
          1540                1545                1550

Pro Gly Ala Gly Val Ser Ser Tyr Ile Ser Gln Pro Gly Gly Leu His
       1555                1560                1565

Pro Leu Val Ile Pro Ser Val Ile Ala Ser Thr Pro Ile Leu Pro Gln
   1570                1575                1580

Ala Ala Gly Pro Thr Ser Thr Pro Leu Leu Pro Gln Val Pro Ser Ile
1585                1590                1595                1600

Pro Pro Leu Val Gln Pro Val Ala Asn Val Pro Ala Val Gln Gln Thr
              1605                1610                1615

Leu Ile His Ser Gln Pro Gln Pro Ala Leu Leu Pro Asn Gln Pro His
          1620                1625                1630

Thr His Cys Pro Glu Val Asp Ser Asp Thr Gln Pro Lys Ala Pro Gly
       1635                1640                1645

Ile Asp Asp Ile Lys Thr Leu Glu Glu Lys Leu Arg Ser Leu Phe Ser
   1650                1655                1660

Glu His Ser Ser Ser Gly Ala Gln His Ala Ser Val Ser Leu Glu Thr
1665                1670                1675                1680

Ser Leu Val Ile Glu Ser Thr Val Thr Pro Gly Ile Pro Thr Thr Ala
              1685                1690                1695

Val Ala Pro Ser Lys Leu Leu Thr Ser Thr Thr Ser Thr Cys Leu Pro
          1700                1705                1710
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Pro Thr Asn Leu Pro Leu Gly Thr Val Ala Leu Pro Val Thr Pro Val
       1715                1720                1725

Val Thr Pro Gly Gln Val Ser Thr Pro Val Ser Thr Thr Thr Ser Gly
   1730                1735                1740

Val Lys Pro Gly Thr Ala Pro Ser Lys Pro Pro Leu Thr Lys Ala Pro
1745                1750                1755                1760

Val Leu Pro Val Gly Thr Glu Leu Pro Ala Gly Thr Leu Pro Ser Glu
               1765                1770                1775

Gln Leu Pro Pro Phe Pro Gly Pro Ser Leu Thr Gln Ser Gln Gln Pro
           1780                1785                1790

Leu Glu Asp Leu Asp Ala Gln Leu Arg Arg Thr Leu Ser Pro Glu Ile
       1795                1800                1805

Ile Thr Val Thr Ser Ala Val Gly Pro Val Ser Met Ala Ala Pro Thr
   1810                1815                1820

Ala Ile Thr Glu Ala Gly Thr Gln Pro Gln Lys Gly Val Ser Gln Val
1825                1830                1835                1840

Lys Glu Gly Pro Val Leu Ala Thr Ser Ser Gly Ala Gly Val Phe Lys
               1845                1850                1855

Met Gly Arg Phe Gln Val Ser Val Ala Ala Asp Gly Ala Gln Lys Glu
           1860                1865                1870

Gly Lys Asn Lys Ser Glu Asp Ala Lys Ser Val His Phe Glu Ser Ser
       1875                1880                1885

Thr Ser Glu Ser Ser Val Leu Ser Ser Ser Ser Pro Glu Ser Thr Leu
   1890                1895                1900

Val Lys Pro Glu Pro Asn Gly Ile Thr Ile Pro Gly Ile Ser Ser Asp
1905                1910                1915                1920

Val Pro Glu Ser Ala His Lys Thr Thr Ala Ser Glu Ala Lys Ser Asp
               1925                1930                1935

Thr Gly Gln Pro Thr Lys Val Gly Arg Phe Gln Val Thr Thr Thr Ala
           1940                1945                1950

Asn Lys Val Gly Arg Phe Ser Val Ser Lys Thr Glu Asp Lys Ile Thr
       1955                1960                1965

Asp Thr Lys Lys Glu Gly Pro Val Ala Ser Pro Pro Phe Met Asp Leu
   1970                1975                1980

Glu Gln Ala Val Leu Pro Ala Val Ile Pro Lys Lys Glu Lys Pro Glu
1985                1990                1995                2000

Leu Ser Glu Pro Ser His Leu Asn Gly Pro Ser Ser Asp Pro Glu Ala
               2005                2010                2015

Ala Phe Leu Ser Arg Asp Val Asp Asp Gly Ser Gly Ser Pro His Ser
           2020                2025                2030

Pro His Gln Leu Ser Ser Lys Ser Leu Pro Ser Gln Asn Leu Ser Gln
       2035                2040                2045

Ser Leu Ser Asn Ser Phe Asn Ser Ser Tyr Met Ser Ser Asp Asn Glu
   2050                2055                2060

Ser Asp Ile Glu Asp Glu Asp Leu Lys Leu Glu Leu Arg Arg Leu Arg
2065                2070                2075                2080

Asp Lys His Leu Lys Glu Ile Gln Asp Leu Gln Ser Arg Gln Lys His
               2085                2090                2095

Glu Ile Glu Ser Leu Tyr Thr Lys Leu Gly Lys Val Pro Pro Ala Val
           2100                2105                2110
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Ile Ile Pro Pro Ala Ala Pro Leu Ser Gly Arg Arg Arg Arg Pro Thr
       2115                2120                2125

Lys Ser Lys Gly Ser Lys Ser Ser Arg Ser Ser Ser Leu Gly Asn Lys
   2130                2135                2140

Ser Pro Gln Leu Ser Gly Asn Leu Ser Gly Gln Ser Ala Ala Ser Val
2145                2150                2155                2160

Leu His Pro Gln Gln Thr Leu His Pro Pro Gly Asn Ile Pro Glu Ser
               2165                2170                2175

Gly Gln Asn Gln Leu Leu Gln Pro Leu Lys Pro Ser Pro Ser Ser Asp
           2180                2185                2190

Asn Leu Tyr Ser Ala Phe Thr Ser Asp Gly Ala Ile Ser Val Pro Ser
       2195                2200                2205

Leu Ser Ala Pro Gly Gln Gly Thr Ser Ser Thr Asn Thr Val Gly Ala
   2210                2215                2220

Thr Val Asn Ser Gln Ala Ala Gln Ala Gln Pro Pro Ala Met Thr Ser
2225                2230                2235                2240

Ser Arg Lys Gly Thr Phe Thr Asp Asp Leu His Lys Leu Val Asp Asn
               2245                2250                2255

Trp Ala Arg Asp Ala Met Asn Leu Ser Gly Arg Arg Gly Ser Lys Gly
           2260                2265                2270

His Met Asn Tyr Glu Gly Pro Gly Met Ala Arg Lys Phe Ser Ala Pro
       2275                2280                2285

Gly Gln Leu Cys Ile Ser Met Thr Ser Asn Leu Gly Gly Ser Ala Pro
   2290                2295                2300

Ile Ser Ala Ala Ser Ala Thr Ser Leu Gly His Phe Thr Lys Ser Met
2305                2310                2315                2320

Cys Pro Pro Gln Gln Tyr Gly Phe Pro Ala Thr Pro Phe Gly Ala Gln
               2325                2330                2335

Trp Ser Gly Thr Gly Gly Pro Ala Pro Gln Pro Leu Gly Gln Phe Gln
           2340                2345                2350

Pro Val Gly Thr Ala Ser Leu Gln Asn Phe Asn Ile Ser Asn Leu Gln
       2355                2360                2365

Lys Ser Ile Ser Asn Pro Pro Gly Ser Asn Leu Arg Thr Thr
   2370                2375                2380


<210> SEQ ID NO 9
<211> LENGTH: 683
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Ser Ser Glu Ser Ser Lys Lys Arg Lys Pro Lys Val Ile Arg Ser
  1               5                  10                  15

Asp Gly Ala Pro Ala Glu Gly Lys Arg Asn Arg Ser Asp Thr Glu Gln
             20                  25                  30

Glu Gly Lys Tyr Tyr Ser Glu Glu Ala Glu Val Asp Leu Arg Asp Pro
         35                  40                  45

Gly Arg Asp Tyr Glu Leu Tyr Lys Tyr Thr Cys Gln Glu Leu Gln Arg
     50                  55                  60

Leu Met Ala Glu Ile Gln Asp Leu Lys Ser Arg Gly Gly Lys Asp Val
 65                  70                  75                  80

Ala Ile Glu Ile Glu Glu Arg Arg Ile Gln Ser Cys Val His Phe Met
                 85                  90                  95
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Thr Leu Lys Lys Leu Asn Arg Leu Ala His Ile Arg Leu Lys Lys Gly
            100                 105                 110

Arg Asp Gln Thr His Glu Ala Lys Gln Lys Val Asp Ala Tyr His Leu
        115                 120                 125

Gln Leu Gln Asn Leu Leu Tyr Glu Val Met His Leu Gln Lys Glu Ile
    130                 135                 140

Thr Lys Cys Leu Glu Phe Lys Ser Lys His Glu Glu Ile Asp Leu Val
145                 150                 155                 160

Ser Leu Glu Glu Phe Tyr Lys Glu Ala Pro Pro Asp Ile Ser Lys Ala
                165                 170                 175

Glu Val Thr Met Gly Asp Pro His Gln Gln Thr Leu Ala Arg Leu Asp
            180                 185                 190

Trp Glu Leu Glu Gln Arg Lys Arg Leu Ala Glu Lys Tyr Arg Glu Cys
        195                 200                 205

Leu Ser Asn Lys Glu Lys Ile Leu Lys Glu Ile Glu Val Lys Lys Glu
    210                 215                 220

Tyr Leu Ser Ser Leu Gln Pro Arg Leu Asn Ser Ile Met Gln Ala Ser
225                 230                 235                 240

Leu Pro Val Gln Glu Tyr Leu Phe Met Pro Phe Asp Gln Ala His Lys
                245                 250                 255

Gln Tyr Glu Thr Ala Arg His Leu Pro Pro Pro Leu Tyr Val Leu Phe
            260                 265                 270

Val Gln Ala Thr Ala Tyr Gly Gln Ala Cys Asp Lys Thr Leu Ser Val
        275                 280                 285

Ala Ile Glu Gly Ser Val Asp Glu Ala Lys Ala Leu Phe Lys Pro Pro
    290                 295                 300

Glu Asp Ser Gln Asp Asp Glu Ser Asp Ser Asp Ala Glu Glu Glu Gln
305                 310                 315                 320

Thr Thr Lys Arg Arg Arg Pro Thr Leu Gly Val Gln Leu Asp Asp Lys
                325                 330                 335

Arg Lys Glu Met Leu Lys Arg His Pro Leu Ser Val Met Leu Asp Leu
            340                 345                 350

Lys Cys Lys Asp Asp Ser Val Leu His Leu Thr Phe Tyr Tyr Leu Met
        355                 360                 365

Asn Leu Asn Ile Met Thr Val Lys Ala Lys Val Thr Thr Ala Met Glu
    370                 375                 380

Leu Ile Thr Pro Ile Ser Ala Gly Asp Leu Leu Ser Pro Asp Ser Val
385                 390                 395                 400

Leu Ser Cys Leu Tyr Pro Gly Asp His Gly Lys Lys Thr Pro Asn Pro
                405                 410                 415

Ala Asn Gln Tyr Gln Phe Asp Lys Val Gly Ile Leu Thr Leu Ser Asp
            420                 425                 430

Tyr Val Leu Glu Leu Gly His Pro Tyr Leu Trp Val Gln Lys Leu Gly
        435                 440                 445

Gly Leu His Phe Pro Lys Glu Gln Pro Gln Gln Thr Val Ile Ala Asp
    450                 455                 460

His Ser Leu Ser Ala Ser His Met Glu Thr Thr Met Lys Leu Leu Lys
465                 470                 475                 480

Thr Arg Val Gln Ser Arg Leu Ala Leu His Lys Gln Phe Ala Ser Leu
                485                 490                 495
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Glu His Gly Ile Val Pro Val Thr Ser Asp Cys Gln Tyr Leu Phe Pro
            500                 505                 510

Ala Lys Val Val Ser Arg Leu Val Lys Trp Val Thr Ile Ala His Glu
        515                 520                 525

Asp Tyr Met Glu Leu His Phe Thr Lys Asp Ile Val Asp Ala Gly Leu
    530                 535                 540

Ala Gly Asp Thr Asn Leu Tyr Tyr Met Ala Leu Ile Glu Arg Gly Thr
545                 550                 555                 560

Ala Lys Leu Gln Ala Ala Val Val Leu Asn Pro Gly Tyr Ser Ser Ile
                565                 570                 575

Pro Pro Val Phe Gln Leu Cys Leu Asn Trp Lys Gly Glu Lys Thr Asn
            580                 585                 590

Ser Asn Asp Asp Asn Ile Arg Ala Met Glu Gly Glu Val Asn Val Cys
        595                 600                 605

Tyr Lys Glu Leu Cys Gly Pro Trp Pro Ser His Gln Leu Leu Thr Asn
    610                 615                 620

Gln Leu Gln Arg Leu Cys Val Leu Leu Asp Val Tyr Leu Glu Thr Glu
625                 630                 635                 640

Ser His Asp Asp Ser Val Glu Gly Pro Lys Glu Phe Pro Gln Glu Lys
                645                 650                 655

Met Cys Leu Arg Leu Phe Arg Gly Pro Ser Arg Met Lys Pro Phe Lys
            660                 665                 670

Tyr Asn His Pro Gln Gly Phe Phe Ser His Arg
        675                 680


<210> SEQ ID NO 10
<211> LENGTH: 967
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Glu Asn Leu Arg Arg Ala Val His Pro Asn Lys Asp Asn Ser Arg
  1               5                  10                  15

Arg Val Glu His Ile Leu Lys Leu Trp Val Ile Glu Ala Lys Asp Leu
             20                  25                  30

Pro Ala Lys Lys Lys Tyr Leu Cys Glu Leu Cys Leu Asp Asp Val Leu
         35                  40                  45

Tyr Ala Arg Thr Thr Gly Lys Leu Lys Thr Asp Asn Val Phe Trp Gly
     50                  55                  60

Glu His Phe Glu Phe His Asn Leu Pro Pro Leu Arg Thr Val Thr Val
 65                  70                  75                  80

His Leu Tyr Arg Glu Thr Asp Lys Lys Lys Lys Lys Glu Arg Asn Ser
                 85                  90                  95

Tyr Leu Gly Leu Val Ser Leu Pro Ala Ala Ser Val Ala Gly Arg Gln
            100                 105                 110

Phe Val Glu Lys Trp Tyr Pro Val Val Thr Pro Asn Pro Lys Gly Gly
        115                 120                 125

Lys Gly Pro Gly Pro Met Ile Arg Ile Lys Ala Arg Tyr Gln Thr Ile
    130                 135                 140

Thr Ile Leu Pro Met Glu Met Tyr Lys Glu Phe Ala Glu His Ile Thr
145                 150                 155                 160

Asn His Tyr Leu Gly Leu Cys Ala Ala Leu Glu Pro Ile Leu Ser Ala
                165                 170                 175
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Lys Thr Lys Glu Glu Met Ala Ser Ala Leu Val His Ile Leu Gln Ser
            180                 185                 190

Thr Gly Lys Val Lys Asp Phe Leu Thr Asp Leu Met Met Ser Glu Val
        195                 200                 205

Asp Arg Cys Gly Asp Asn Glu His Leu Ile Phe Arg Glu Asn Thr Leu
    210                 215                 220

Ala Thr Lys Ala Ile Glu Glu Tyr Leu Lys Leu Val Gly Gln Lys Tyr
225                 230                 235                 240

Leu Gln Asp Ala Leu Gly Glu Phe Ile Lys Ala Leu Tyr Glu Ser Asp
                245                 250                 255

Glu Asn Cys Glu Val Asp Pro Ser Lys Cys Ser Ala Ala Asp Leu Pro
            260                 265                 270

Glu His Gln Gly Asn Leu Lys Met Cys Cys Glu Leu Ala Phe Cys Lys
        275                 280                 285

Thr Ile Asn Ser Tyr Cys Val Phe Pro Arg Glu Leu Lys Glu Val Phe
    290                 295                 300

Ala Ser Trp Arg Gln Glu Cys Ser Ser Arg Gly Arg Pro Asp Ile Ser
305                 310                 315                 320

Glu Arg Leu Ile Ser Ala Ser Leu Phe Leu Arg Phe Leu Cys Pro Ala
                325                 330                 335

Ile Met Ser Pro Ser Leu Phe Asn Leu Leu Gln Glu Tyr Pro Asp Asp
            340                 345                 350

Arg Thr Ala Arg Thr Leu Thr Leu Ile Ala Lys Val Thr Gln Asn Leu
        355                 360                 365

Ala Asn Phe Ala Lys Phe Gly Ser Lys Glu Glu Tyr Met Ser Phe Met
    370                 375                 380

Asn Gln Phe Leu Glu His Glu Trp Thr Asn Met Gln Arg Phe Leu Leu
385                 390                 395                 400

Glu Ile Ser Asn Pro Glu Thr Leu Ser Asn Thr Ala Gly Phe Glu Gly
                405                 410                 415

Tyr Ile Asp Leu Gly Arg Glu Leu Ser Ser Leu His Ser Leu Leu Trp
            420                 425                 430

Glu Ala Val Ser Gln Leu Glu Gln Ser Ile Val Ser Lys Leu Gly Pro
        435                 440                 445

Leu Pro Arg Ile Leu Arg Asp Val His Thr Ala Leu Ser Thr Pro Gly
    450                 455                 460

Ser Gly Gln Leu Pro Gly Thr Asn Asp Leu Ala Ser Thr Pro Gly Ser
465                 470                 475                 480

Gly Ser Ser Ser Ile Ser Ala Gly Leu Gln Lys Met Val Ile Glu Asn
                485                 490                 495

Asp Leu Ser Gly Leu Ile Asp Phe Thr Arg Leu Pro Ser Pro Thr Pro
            500                 505                 510

Glu Asn Lys Asp Leu Phe Phe Val Thr Arg Ser Ser Gly Val Gln Pro
        515                 520                 525

Ser Pro Ala Arg Ser Ser Ser Tyr Ser Glu Ala Asn Glu Pro Asp Leu
    530                 535                 540

Gln Met Ala Asn Gly Gly Lys Ser Leu Ser Met Val Asp Leu Gln Asp
545                 550                 555                 560

Ala Arg Thr Leu Asp Gly Glu Ala Gly Ser Pro Ala Gly Pro Asp Val
                565                 570                 575
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Leu Pro Thr Asp Gly Gln Ala Ala Ala Ala Gln Leu Val Ala Gly Trp
            580                 585                 590

Pro Ala Arg Ala Thr Pro Val Asn Leu Ala Gly Leu Ala Thr Val Arg
        595                 600                 605

Arg Ala Gly Gln Thr Pro Thr Thr Pro Gly Thr Ser Glu Gly Ala Pro
    610                 615                 620

Gly Arg Pro Gln Leu Leu Ala Pro Leu Ser Phe Gln Asn Pro Val Tyr
625                 630                 635                 640

Gln Met Ala Ala Gly Leu Pro Leu Ser Pro Arg Gly Leu Gly Asp Ser
                645                 650                 655

Gly Ser Glu Gly His Ser Ser Leu Ser Ser His Ser Asn Ser Glu Glu
            660                 665                 670

Leu Ala Ala Ala Ala Lys Leu Gly Ser Phe Ser Thr Ala Ala Glu Glu
        675                 680                 685

Leu Ala Arg Arg Pro Gly Glu Leu Ala Arg Arg Gln Met Ser Leu Thr
    690                 695                 700

Glu Lys Gly Gly Gln Pro Thr Val Pro Arg Gln Asn Ser Ala Gly Pro
705                 710                 715                 720

Gln Arg Arg Ile Asp Gln Pro Ser Pro Pro Pro Pro Pro Pro Pro Pro
                725                 730                 735

Ala Pro Arg Gly Arg Thr Pro Pro Asn Leu Leu Ser Thr Leu Gln Tyr
            740                 745                 750

Pro Arg Pro Ser Ser Gly Thr Leu Ala Ser Ala Ser Pro Asp Trp Val
        755                 760                 765

Gly Pro Ser Thr Arg Leu Arg Gln Gln Ser Ser Ser Ser Lys Gly Asp
    770                 775                 780

Ser Pro Glu Leu Lys Pro Arg Ala Val His Lys Gln Gly Pro Ser Pro
785                 790                 795                 800

Val Ser Pro Asn Ala Leu Asp Arg Thr Ala Ala Trp Leu Leu Thr Met
                805                 810                 815

Asn Ala Gln Leu Leu Glu Asp Glu Gly Leu Gly Pro Asp Pro Pro His
            820                 825                 830

Arg Asp Arg Leu Arg Ser Lys Asp Glu Leu Ser Gln Ala Glu Lys Asp
        835                 840                 845

Leu Ala Val Leu Gln Asp Lys Leu Arg Ile Ser Thr Lys Lys Leu Glu
    850                 855                 860

Glu Tyr Glu Thr Leu Phe Lys Cys Gln Glu Glu Thr Thr Gln Lys Leu
865                 870                 875                 880

Val Leu Glu Tyr Gln Ala Arg Leu Glu Glu Gly Glu Glu Arg Leu Arg
                885                 890                 895

Arg His Glu Glu Asp Lys Asp Ile Gln Met Lys Gly Ile Ile Ser Arg
            900                 905                 910

Leu Met Ser Val Glu Glu Glu Leu Lys Lys Asp His Ala Glu Met Gln
        915                 920                 925

Ala Ala Val Asp Ser Lys Gln Lys Ile Ile Asp Ala Gln Glu Lys Arg
    930                 935                 940

Ile Ala Ser Leu Asp Ala Ala Asn Ala Arg Leu Met Ser Ala Leu Thr
945                 950                 955                 960

Gln Leu Lys Glu Ser Met His
                965
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<210> SEQ ID NO 11
<211> LENGTH: 657
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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

Phe Thr Lys Ser Thr Arg Glu Ala Leu Asn Asn Lys Asn Ile Lys Pro
             20                  25                  30

Leu Leu Ser Thr Phe Ser Gln Val Pro Gly Ser Glu Asn Glu Lys Lys
         35                  40                  45

Cys Thr Leu Asp Gln Ala Phe Arg Gly Ile Leu Glu Glu Glu Ile Ile
     50                  55                  60

Asn His Ser Ser Cys Glu Asn Val Leu Ala Ile Ile Ser Leu Ala Ile
 65                  70                  75                  80

Gly Gly Val Thr Glu Gly Ile Cys Thr Ala Ser Thr Pro Phe Val Leu
                 85                  90                  95

Leu Gly Asp Val Leu Asp Cys Leu Pro Leu Asp Gln Cys Asp Thr Ile
            100                 105                 110

Phe Thr Phe Val Glu Lys Asn Val Ala Thr Trp Lys Ser Asn Thr Phe
        115                 120                 125

Tyr Ala Ala Gly Lys Asn Tyr Leu Leu Arg Met Cys Asn Asp Leu Leu
    130                 135                 140

Arg Arg Leu Ser Lys Ser Gln Asn Thr Val Phe Cys Gly Arg Ile Gln
145                 150                 155                 160

Leu Phe Leu Ala Arg Leu Phe Pro Leu Ser Glu Lys Ser Gly Leu Asn
                165                 170                 175

Leu Gln Ser Gln Phe Asn Leu Glu Asn Val Thr Val Phe Asn Thr Asn
            180                 185                 190

Glu Gln Glu Ser Thr Leu Gly Gln Lys His Thr Glu Asp Arg Glu Glu
        195                 200                 205

Gly Met Asp Val Glu Glu Gly Glu Met Gly Asp Glu Glu Ala Pro Thr
    210                 215                 220

Thr Cys Ser Ile Pro Ile Asp Tyr Asn Leu Tyr Arg Lys Phe Trp Ser
225                 230                 235                 240

Leu Gln Asp Tyr Phe Arg Asn Pro Val Gln Cys Tyr Glu Lys Ile Ser
                245                 250                 255

Trp Lys Thr Phe Leu Lys Tyr Ser Glu Glu Val Leu Ala Val Phe Lys
            260                 265                 270

Ser Tyr Lys Leu Asp Asp Thr Gln Ala Ser Arg Lys Lys Met Glu Glu
        275                 280                 285

Leu Lys Thr Gly Gly Glu His Val Tyr Phe Ala Lys Phe Leu Thr Ser
    290                 295                 300

Glu Lys Leu Met Asp Leu Gln Leu Ser Asp Ser Asn Phe Arg Arg His
305                 310                 315                 320

Ile Leu Leu Gln Tyr Leu Ile Leu Phe Gln Tyr Leu Lys Gly Gln Val
                325                 330                 335

Lys Phe Lys Ser Ser Asn Tyr Val Leu Thr Asp Glu Gln Ser Leu Trp
            340                 345                 350

Ile Glu Asp Thr Thr Lys Ser Val Tyr Gln Leu Leu Ser Glu Asn Pro
        355                 360                 365
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Pro Asp Gly Glu Arg Phe Ser Lys Met Val Glu His Ile Leu Asn Thr
    370                 375                 380

Glu Glu Asn Trp Asn Ser Trp Lys Asn Glu Gly Cys Pro Ser Phe Val
385                 390                 395                 400

Lys Glu Arg Thr Ser Asp Thr Lys Pro Thr Arg Ile Ile Arg Lys Arg
                405                 410                 415

Thr Ala Pro Glu Asp Phe Leu Gly Lys Gly Pro Thr Lys Lys Ile Leu
            420                 425                 430

Thr Gly Asn Glu Glu Leu Thr Arg Leu Trp Asn Leu Cys Pro Asp Asn
        435                 440                 445

Met Glu Ala Cys Lys Ser Glu Thr Arg Glu His Met Pro Thr Leu Glu
    450                 455                 460

Glu Phe Phe Glu Glu Ala Ile Glu Gln Ala Asp Pro Glu Asn Met Ala
465                 470                 475                 480

Glu Asn Glu Tyr Lys Ala Met Asn Asn Ser Asn Tyr Gly Trp Arg Ala
                485                 490                 495

Leu Lys Leu Leu Ala Arg Arg Ser Pro His Phe Phe Gln Pro Thr Asn
            500                 505                 510

Gln Gln Phe Lys Ser Leu Gln Glu Tyr Leu Glu Asn Met Val Ile Lys
        515                 520                 525

Leu Ala Lys Glu Leu Pro Pro Pro Ser Glu Glu Ile Lys Thr Gly Glu
    530                 535                 540

Asp Glu Asp Glu Glu Asp Asn Asp Ala Leu Leu Lys Glu Asn Glu Ser
545                 550                 555                 560

Pro Asp Val Arg Arg Asp Lys Pro Val Thr Gly Glu Gln Ile Glu Val
                565                 570                 575

Phe Ala Asn Lys Leu Gly Glu Gln Trp Lys Ile Leu Ala Pro Tyr Leu
            580                 585                 590

Glu Met Lys Asp Ser Glu Ile Arg Gln Ile Glu Cys Asp Ser Glu Asp
        595                 600                 605

Met Lys Met Arg Ala Lys Gln Leu Leu Val Ala Trp Gln Asp Gln Glu
    610                 615                 620

Gly Val His Ala Thr Pro Glu Asn Leu Ile Asn Ala Leu Asn Lys Ser
625                 630                 635                 640

Gly Leu Ser Asp Leu Ala Glu Ser Leu Thr Asn Asp Asn Glu Thr Asn
                645                 650                 655

Ser


<210> SEQ ID NO 12
<211> LENGTH: 556
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Met Ala Arg Glu Lys Glu Met Gln Glu Phe Thr Arg Ser Phe Phe Arg
  1               5                  10                  15

Gly Arg Pro Asp Leu Ser Thr Leu Thr His Ser Ile Val Arg Arg Arg
             20                  25                  30

Tyr Leu Ala His Ser Gly Arg Ser His Leu Glu Pro Glu Glu Lys Gln
         35                  40                  45

Ala Leu Lys Arg Leu Val Glu Glu Glu Leu Leu Lys Met Gln Val Asp
     50                  55                  60
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Glu Ala Ala Ser Arg Glu Asp Lys Leu Asp Leu Thr Lys Lys Gly Lys
 65                  70                  75                  80

Arg Pro Pro Thr Pro Cys Ser Asp Pro Glu Arg Lys Arg Phe Arg Phe
                 85                  90                  95

Asn Ser Glu Ser Glu Ser Gly Ser Glu Ala Ser Ser Pro Asp Tyr Phe
            100                 105                 110

Gly Pro Pro Ala Lys Asn Gly Val Ala Ala Glu Val Ser Pro Ala Lys
        115                 120                 125

Glu Glu Asn Pro Arg Arg Ala Ser Lys Ala Val Glu Glu Ser Ser Asp
    130                 135                 140

Glu Glu Arg Gln Arg Asp Leu Pro Ala Gln Arg Gly Glu Glu Ser Ser
145                 150                 155                 160

Glu Glu Glu Glu Lys Gly Tyr Lys Gly Lys Thr Arg Lys Lys Pro Val
                165                 170                 175

Val Lys Lys Gln Ala Pro Gly Lys Ala Ser Val Ser Arg Lys Gln Ala
            180                 185                 190

Arg Glu Glu Ser Glu Glu Ser Glu Ala Glu Pro Val Gln Arg Thr Ala
        195                 200                 205

Lys Lys Val Glu Gly Asn Lys Gly Thr Lys Ser Leu Lys Glu Ser Glu
    210                 215                 220

Gln Glu Ser Glu Glu Glu Ile Leu Ala Gln Lys Lys Glu Gln Arg Glu
225                 230                 235                 240

Glu Glu Val Glu Glu Glu Glu Lys Glu Glu Asp Glu Glu Lys Gly Asp
                245                 250                 255

Trp Lys Pro Arg Thr Arg Ser Asn Gly Arg Arg Lys Ser Ala Arg Glu
            260                 265                 270

Glu Arg Ser Cys Lys Gln Lys Ser Gln Ala Lys Arg Leu Leu Gly Asp
        275                 280                 285

Ser Asp Ser Glu Glu Glu Gln Lys Glu Ala Ala Ser Ser Gly Asp Asp
    290                 295                 300

Ser Gly Arg Asp Arg Glu Pro Pro Val Gln Arg Lys Ser Glu Asp Arg
305                 310                 315                 320

Thr Gln Leu Lys Gly Gly Lys Arg Leu Ser Gly Ser Ser Glu Asp Glu
                325                 330                 335

Glu Asp Ser Gly Lys Gly Glu Pro Thr Ala Lys Gly Ser Arg Lys Met
            340                 345                 350

Ala Arg Leu Gly Ser Thr Ser Gly Glu Glu Ser Asp Leu Glu Arg Glu
        355                 360                 365

Val Ser Asp Ser Glu Ala Gly Gly Gly Pro Gln Gly Glu Arg Lys Asn
    370                 375                 380

Arg Ser Ser Lys Lys Ser Ser Arg Lys Gly Arg Thr Arg Ser Ser Ser
385                 390                 395                 400

Ser Ser Ser Asp Gly Ser Pro Glu Ala Lys Gly Gly Lys Ala Gly Ser
                405                 410                 415

Gly Arg Arg Gly Glu Asp His Pro Ala Val Met Arg Leu Lys Arg Tyr
            420                 425                 430

Ile Arg Ala Cys Gly Ala His Arg Asn Tyr Lys Lys Leu Leu Gly Ser
        435                 440                 445

Cys Cys Ser His Lys Glu Arg Leu Ser Ile Leu Arg Ala Glu Leu Glu
    450                 455                 460

Ala Leu Gly Met Lys Gly Thr Pro Ser Leu Gly Lys Cys Arg Ala Leu
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465                 470                 475                 480

Lys Glu Gln Arg Glu Glu Ala Ala Glu Val Ala Ser Leu Asp Val Ala
                485                 490                 495

Asn Ile Ile Ser Gly Ser Gly Arg Pro Arg Arg Arg Thr Ala Trp Asn
            500                 505                 510

Pro Leu Gly Glu Ala Ala Pro Pro Gly Glu Leu Tyr Arg Arg Thr Leu
        515                 520                 525

Asp Ser Asp Glu Glu Arg Pro Arg Pro Ala Pro Pro Asp Trp Ser His
    530                 535                 540

Met Arg Gly Ile Ile Ser Ser Asp Gly Glu Ser Asn
545                 550                 555


<210> SEQ ID NO 13
<211> LENGTH: 493
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Met Ser Lys Gly Pro Ala Val Gly Ile Asp Leu Gly Thr Thr Tyr Ser
  1               5                  10                  15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
             20                  25                  30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
         35                  40                  45

Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Met Asn Pro Thr
     50                  55                  60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp
 65                  70                  75                  80

Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn
                 85                  90                  95

Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys
            100                 105                 110

Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys
        115                 120                 125

Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val
    130                 135                 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
145                 150                 155                 160

Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
                165                 170                 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Lys Lys Val Gly Ala Glu
            180                 185                 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
        195                 200                 205

Ile Leu Thr Ile Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly
    210                 215                 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Met Val Asn His
225                 230                 235                 240

Phe Ile Ala Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Glu Asn
                245                 250                 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
            260                 265                 270
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Thr Leu Ser Ser Ser Thr Gln Ala Ser Ile Glu Ile Asp Ser Leu Tyr
        275                 280                 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
    290                 295                 300

Leu Asn Ala Asp Leu Phe Arg Gly Thr Leu Asp Pro Val Glu Lys Ala
305                 310                 315                 320

Leu Arg Asp Ala Lys Leu Asp Lys Ser Gln Ile His Asp Ile Val Leu
                325                 330                 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Ile Gln Lys Leu Leu Gln Asp
            340                 345                 350

Phe Phe Asn Gly Lys Glu Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
        355                 360                 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Ser Gly Asp Lys
    370                 375                 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Thr Pro Leu Ser
385                 390                 395                 400

Leu Gly Ile Glu Thr Ala Gly Gly Val Met Thr Val Leu Ile Lys Arg
                405                 410                 415

Asn Thr Thr Ile Pro Thr Lys Gln Thr Gln Thr Phe Thr Thr Tyr Ser
            420                 425                 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
        435                 440                 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Lys Phe Glu Leu Thr Gly Met
    450                 455                 460

Pro Gly Gly Met Pro Gly Gly Phe Pro Gly Gly Gly Ala Pro Pro Ser
465                 470                 475                 480

Gly Gly Ala Ser Ser Gly Pro Thr Ile Glu Glu Val Asp
                485                 490


<210> SEQ ID NO 14
<211> LENGTH: 646
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Ser Lys Gly Pro Ala Val Gly Ile Asp Leu Gly Thr Thr Tyr Ser
  1               5                  10                  15

Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
             20                  25                  30

Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
         35                  40                  45

Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Met Asn Pro Thr
     50                  55                  60

Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp
 65                  70                  75                  80

Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn
                 85                  90                  95

Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys
            100                 105                 110

Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys
        115                 120                 125

Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val
    130                 135                 140
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Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
145                 150                 155                 160

Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
                165                 170                 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Lys Lys Val Gly Ala Glu
            180                 185                 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
        195                 200                 205

Ile Leu Thr Ile Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly
    210                 215                 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Met Val Asn His
225                 230                 235                 240

Phe Ile Ala Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Glu Asn
                245                 250                 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
            260                 265                 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Ile Glu Ile Asp Ser Leu Tyr
        275                 280                 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
    290                 295                 300

Leu Asn Ala Asp Leu Phe Arg Gly Thr Leu Asp Pro Val Glu Lys Ala
305                 310                 315                 320

Leu Arg Asp Ala Lys Leu Asp Lys Ser Gln Ile His Asp Ile Val Leu
                325                 330                 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Ile Gln Lys Leu Leu Gln Asp
            340                 345                 350

Phe Phe Asn Gly Lys Glu Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
        355                 360                 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Ser Gly Asp Lys
    370                 375                 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Thr Pro Leu Ser
385                 390                 395                 400

Leu Gly Ile Glu Thr Ala Gly Gly Val Met Thr Val Leu Ile Lys Arg
                405                 410                 415

Asn Thr Thr Ile Pro Thr Lys Gln Thr Gln Thr Phe Thr Thr Tyr Ser
            420                 425                 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
        435                 440                 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Lys Phe Glu Leu Thr Gly Ile
    450                 455                 460

Pro Pro Ala Pro Arg Gly Val Pro Gln Ile Glu Val Thr Phe Asp Ile
465                 470                 475                 480

Asp Ala Asn Gly Ile Leu Asn Val Ser Ala Val Asp Lys Ser Thr Gly
                485                 490                 495

Lys Glu Asn Lys Ile Thr Ile Thr Asn Asp Lys Gly Arg Leu Ser Lys
            500                 505                 510

Glu Asp Ile Glu Arg Met Val Gln Glu Ala Glu Lys Tyr Lys Ala Glu
        515                 520                 525

Asp Glu Lys Gln Arg Asp Lys Val Ser Ser Lys Asn Ser Leu Glu Ser
    530                 535                 540
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```
Tyr Ala Phe Asn Met Lys Ala Thr Val Glu Asp Glu Lys Leu Gln Gly
545                 550                 555                 560

Lys Ile Asn Asp Glu Asp Lys Gln Lys Ile Leu Asp Lys Cys Asn Glu
                565                 570                 575

Ile Ile Asn Trp Leu Asp Lys Asn Gln Thr Ala Glu Lys Glu Glu Phe
            580                 585                 590

Glu His Gln Gln Lys Glu Leu Glu Lys Val Cys Asn Pro Ile Ile Thr
        595                 600                 605

Lys Leu Tyr Gln Ser Ala Gly Gly Met Pro Gly Gly Met Pro Gly Gly
    610                 615                 620

Phe Pro Gly Gly Gly Ala Pro Pro Ser Gly Gly Ala Ser Ser Gly Pro
625                 630                 635                 640

Thr Ile Glu Glu Val Asp
                645


<210> SEQ ID NO 15
<211> LENGTH: 288
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Ala Gly Glu Lys Val Glu Lys Pro Asp Thr Lys Glu Lys Lys Pro
  1               5                  10                  15

Glu Ala Lys Lys Val Asp Ala Gly Gly Lys Val Lys Lys Gly Asn Leu
             20                  25                  30

Lys Ala Lys Lys Pro Lys Lys Gly Lys Pro His Cys Ser Arg Asn Pro
         35                  40                  45

Val Leu Val Arg Gly Ile Gly Arg Tyr Ser Arg Ser Ala Met Tyr Ser
     50                  55                  60

Arg Lys Ala Met Tyr Lys Arg Lys Tyr Ser Ala Ala Lys Ser Lys Val
 65                  70                  75                  80

Glu Lys Lys Lys Lys Glu Lys Val Leu Ala Thr Val Thr Lys Pro Val
                 85                  90                  95

Gly Gly Asp Lys Asn Gly Gly Thr Arg Val Val Lys Leu Arg Lys Met
            100                 105                 110

Pro Arg Tyr Tyr Pro Thr Glu Asp Val Pro Arg Lys Leu Leu Ser His
        115                 120                 125

Gly Lys Lys Pro Phe Ser Gln His Val Arg Lys Leu Arg Ala Ser Ile
    130                 135                 140

Thr Pro Gly Thr Ile Leu Ile Ile Leu Thr Gly Arg His Arg Gly Lys
145                 150                 155                 160

Arg Val Val Phe Leu Lys Gln Leu Ala Ser Gly Leu Leu Leu Val Thr
                165                 170                 175

Gly Pro Leu Val Leu Asn Arg Val Pro Leu Arg Arg Thr His Gln Lys
            180                 185                 190

Phe Val Ile Ala Thr Ser Thr Lys Ile Asp Ile Ser Asn Val Lys Ile
        195                 200                 205

Pro Lys His Leu Thr Asp Ala Tyr Phe Lys Lys Lys Lys Leu Arg Lys
    210                 215                 220

Pro Arg His Gln Glu Gly Glu Ile Phe Asp Thr Glu Lys Glu Lys Tyr
225                 230                 235                 240

Glu Ile Thr Glu Gln Arg Lys Ile Asp Gln Lys Ala Val Asp Ser Gln
                245                 250                 255
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```
Ile Leu Pro Lys Ile Lys Ala Ile Pro Gln Leu Gln Gly Tyr Leu Arg
            260                 265                 270

Ser Val Phe Ala Leu Thr Asn Gly Ile Tyr Pro His Lys Leu Val Phe
        275                 280                 285


<210> SEQ ID NO 16
<211> LENGTH: 2813
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Lys Leu Asn Pro Gln Gln Ala Pro Leu Tyr Gly Asp Cys Val Val
  1               5                  10                  15

Thr Val Leu Leu Ala Glu Glu Asp Lys Ala Glu Asp Asp Val Val Phe
             20                  25                  30

Tyr Leu Val Phe Leu Gly Ser Thr Leu Arg His Cys Thr Ser Thr Arg
         35                  40                  45

Lys Val Ser Ser Asp Thr Leu Glu Thr Ile Ala Pro Gly His Asp Cys
     50                  55                  60

Cys Glu Thr Val Lys Val Gln Leu Cys Ala Ser Lys Glu Gly Leu Pro
 65                  70                  75                  80

Val Phe Val Val Ala Glu Glu Asp Phe His Phe Val Gln Asp Glu Ala
                 85                  90                  95

Tyr Asp Ala Ala Gln Phe Leu Ala Thr Ser Ala Gly Asn Gln Gln Ala
            100                 105                 110

Leu Asn Phe Thr Arg Phe Leu Asp Gln Ser Gly Pro Pro Ser Gly Asp
        115                 120                 125

Val Asn Ser Leu Asp Lys Lys Leu Val Leu Ala Phe Arg His Leu Lys
    130                 135                 140

Leu Pro Thr Glu Trp Asn Val Leu Gly Thr Asp Gln Ser Leu His Asp
145                 150                 155                 160

Ala Gly Pro Arg Glu Thr Leu Met His Phe Ala Val Arg Leu Gly Leu
                165                 170                 175

Leu Arg Leu Thr Trp Phe Leu Leu Gln Lys Pro Gly Gly Arg Gly Ala
            180                 185                 190

Leu Ser Ile His Asn Gln Glu Gly Ala Thr Pro Val Ser Leu Ala Leu
        195                 200                 205

Glu Arg Gly Tyr His Lys Leu His Gln Leu Leu Thr Glu Glu Asn Ala
    210                 215                 220

Gly Glu Pro Asp Ser Trp Ser Ser Leu Ser Tyr Glu Ile Pro Tyr Gly
225                 230                 235                 240

Asp Cys Ser Val Arg His His Arg Glu Leu Asp Ile Tyr Thr Leu Thr
                245                 250                 255

Ser Glu Ser Asp Ser His His Glu His Pro Phe Pro Gly Asp Gly Cys
            260                 265                 270

Thr Gly Pro Ile Phe Lys Leu Met Asn Ile Gln Gln Gln Leu Met Lys
        275                 280                 285

Thr Asn Leu Lys Gln Met Asp Ser Leu Met Pro Leu Met Met Thr Ala
    290                 295                 300

Gln Asp Pro Ser Ser Ala Pro Glu Thr Asp Gly Gln Phe Leu Pro Cys
305                 310                 315                 320

Ala Pro Glu Pro Thr Asp Pro Gln Arg Leu Ser Ser Ser Glu Glu Thr
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               325                 330                 335

Glu Ser Thr Gln Cys Cys Pro Gly Ser Pro Val Ala Gln Thr Glu Ser
            340                 345                 350

Pro Cys Asp Leu Ser Ser Ile Val Glu Glu Glu Asn Thr Asp Arg Ser
        355                 360                 365

Cys Arg Lys Lys Asn Lys Gly Val Glu Arg Lys Gly Glu Glu Val Glu
    370                 375                 380

Pro Ala Pro Ile Val Asp Ser Gly Thr Val Ser Asp Gln Asp Ser Cys
385                 390                 395                 400

Leu Gln Ser Leu Pro Asp Cys Gly Val Lys Gly Thr Glu Gly Leu Ser
                405                 410                 415

Ser Cys Gly Asn Arg Asn Glu Glu Thr Gly Thr Lys Ser Ser Gly Met
            420                 425                 430

Pro Thr Asp Gln Glu Ser Leu Ser Ser Gly Asp Ala Val Leu Gln Arg
        435                 440                 445

Asp Leu Val Met Glu Pro Gly Thr Ala Gln Tyr Ser Ser Gly Gly Glu
    450                 455                 460

Leu Gly Gly Ile Ser Thr Thr Asn Val Ser Thr Pro Asp Thr Ala Gly
465                 470                 475                 480

Glu Met Glu His Gly Leu Met Asn Pro Asp Ala Thr Val Trp Lys Asn
                485                 490                 495

Val Leu Gln Gly Gly Glu Ser Thr Lys Glu Arg Phe Glu Asn Ser Asn
            500                 505                 510

Ile Gly Thr Ala Gly Ala Ser Asp Val His Val Thr Ser Lys Pro Val
        515                 520                 525

Asp Lys Ile Ser Val Pro Asn Cys Ala Pro Ala Ala Ser Ser Leu Asp
    530                 535                 540

Gly Asn Lys Pro Ala Glu Ser Ser Leu Ala Phe Ser Asn Glu Glu Thr
545                 550                 555                 560

Ser Thr Glu Lys Thr Ala Glu Thr Glu Thr Ser Arg Ser Arg Glu Glu
                565                 570                 575

Ser Ala Asp Ala Pro Val Asp Gln Asn Ser Val Val Ile Pro Ala Ala
            580                 585                 590

Ala Lys Asp Lys Ile Ser Asp Gly Leu Glu Pro Tyr Thr Leu Leu Ala
        595                 600                 605

Ala Gly Ile Gly Glu Ala Met Ser Pro Ser Asp Leu Ala Leu Leu Gly
    610                 615                 620

Leu Glu Glu Asp Val Met Pro His Gln Asn Ser Glu Thr Asn Ser Ser
625                 630                 635                 640

His Ala Gln Ser Gln Lys Gly Lys Ser Ser Pro Ile Cys Ser Thr Thr
                645                 650                 655

Gly Asp Asp Lys Leu Cys Ala Asp Ser Ala Cys Gln Gln Asn Thr Val
            660                 665                 670

Thr Ser Ser Gly Asp Leu Val Ala Lys Leu Cys Asp Asn Ile Val Ser
        675                 680                 685

Glu Ser Glu Ser Thr Thr Ala Arg Gln Pro Ser Ser Gln Asp Pro Pro
    690                 695                 700

Asp Ala Ser His Cys Glu Asp Pro Gln Ala His Thr Val Thr Ser Asp
705                 710                 715                 720

Pro Val Arg Asp Thr Gln Glu Arg Ala Asp Phe Cys Pro Phe Lys Val
                725                 730                 735
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Val Asp Asn Lys Gly Gln Arg Lys Asp Val Lys Leu Asp Lys Pro Leu
            740                 745                 750

Thr Asn Met Leu Glu Val Val Ser His Pro His Pro Val Val Pro Lys
        755                 760                 765

Met Glu Lys Glu Leu Val Pro Asp Gln Ala Val Ile Ser Asp Ser Thr
    770                 775                 780

Phe Ser Leu Ala Asn Ser Pro Gly Ser Glu Ser Val Thr Lys Asp Asp
785                 790                 795                 800

Ala Leu Ser Phe Val Pro Ser Gln Lys Glu Lys Gly Thr Ala Thr Pro
                805                 810                 815

Glu Leu His Thr Ala Thr Asp Tyr Arg Asp Gly Pro Asp Gly Asn Ser
            820                 825                 830

Asn Glu Pro Asp Thr Arg Pro Leu Glu Asp Arg Ala Val Gly Leu Ser
        835                 840                 845

Thr Ser Ser Thr Ala Ala Glu Leu Gln His Gly Met Gly Asn Thr Ser
    850                 855                 860

Leu Thr Gly Leu Gly Gly Glu His Glu Gly Pro Ala Pro Pro Ala Ile
865                 870                 875                 880

Pro Glu Ala Leu Asn Ile Lys Gly Asn Thr Asp Ser Ser Leu Gln Ser
                885                 890                 895

Val Gly Lys Ala Thr Leu Ala Leu Asp Ser Val Leu Thr Glu Glu Gly
            900                 905                 910

Lys Leu Leu Val Val Ser Glu Ser Ser Ala Ala Gln Glu Gln Asp Lys
        915                 920                 925

Asp Lys Ala Val Thr Cys Ser Ser Ile Lys Glu Asn Ala Leu Ser Ser
    930                 935                 940

Gly Thr Leu Gln Glu Glu Gln Arg Thr Pro Pro Pro Gly Gln Asp Thr
945                 950                 955                 960

Gln Gln Phe His Glu Lys Ser Ile Ser Ala Asp Cys Ala Lys Asp Lys
                965                 970                 975

Ala Leu Gln Leu Ser Asn Ser Pro Gly Ala Ser Ser Ala Phe Leu Lys
            980                 985                 990

Ala Glu Thr Glu His Asn Lys Glu Val Ala Pro Gln Val Ser Leu Leu
        995                1000                1005

Thr Gln Gly Gly Ala Ala Gln Ser Leu Val Pro Pro Gly Ala Ser Leu
   1010                1015                1020

Ala Thr Glu Ser Arg Gln Glu Ala Leu Gly Ala Glu His Asn Ser Ser
1025                1030                1035                1040

Ala Leu Leu Pro Cys Leu Leu Pro Asp Gly Ser Asp Gly Ser Asp Ala
               1045                1050                1055

Leu Asn Cys Ser Gln Pro Ser Pro Leu Asp Val Gly Val Lys Asn Thr
           1060                1065                1070

Gln Ser Gln Gly Lys Thr Ser Ala Cys Glu Val Ser Gly Asp Val Thr
       1075                1080                1085

Val Asp Val Thr Gly Val Asn Ala Leu Gln Gly Met Ala Glu Pro Arg
   1090                1095                1100

Arg Glu Asn Ile Ser His Asn Thr Gln Asp Ile Leu Ile Pro Asn Val
1105                1110                1115                1120

Leu Leu Ser Gln Glu Lys Asn Ala Val Leu Gly Leu Pro Val Ala Leu
               1125                1130                1135
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Gln Asp Lys Ala Val Thr Asp Pro Gln Gly Val Gly Thr Pro Glu Met
          1140                1145                1150

Ile Pro Leu Asp Trp Glu Lys Gly Lys Leu Glu Gly Ala Asp His Ser
       1155                1160                1165

Cys Thr Met Gly Asp Ala Glu Glu Ala Gln Ile Asp Asp Glu Ala His
   1170                1175                1180

Pro Val Leu Leu Gln Pro Val Ala Lys Glu Leu Pro Thr Asp Met Glu
1185                1190                1195                1200

Leu Ser Ala His Asp Asp Gly Ala Pro Ala Gly Val Arg Glu Val Met
               1205                1210                1215

Arg Ala Pro Pro Ser Gly Arg Glu Arg Ser Thr Pro Ser Leu Pro Cys
          1220                1225                1230

Met Val Ser Ala Gln Asp Ala Pro Leu Pro Lys Gly Ala Asp Leu Ile
       1235                1240                1245

Glu Glu Ala Ala Ser Arg Ile Val Asp Ala Val Ile Glu Gln Val Lys
   1250                1255                1260

Ala Ala Gly Ala Leu Leu Thr Glu Gly Glu Ala Cys His Met Ser Leu
1265                1270                1275                1280

Ser Ser Pro Glu Leu Gly Pro Leu Thr Lys Gly Leu Glu Ser Ala Phe
               1285                1290                1295

Thr Glu Lys Val Ser Thr Phe Pro Pro Gly Glu Ser Leu Pro Met Gly
          1300                1305                1310

Ser Thr Pro Glu Glu Ala Thr Gly Ser Leu Ala Gly Cys Phe Ala Gly
       1315                1320                1325

Arg Glu Glu Pro Glu Lys Ile Ile Leu Pro Val Gln Gly Pro Glu Pro
   1330                1335                1340

Ala Ala Glu Met Pro Asp Val Lys Ala Glu Asp Glu Val Asp Phe Arg
1345                1350                1355                1360

Ala Ser Ser Ile Ser Glu Glu Val Ala Val Gly Ser Ile Ala Ala Thr
               1365                1370                1375

Leu Lys Met Lys Gln Gly Pro Met Thr Gln Ala Ile Asn Arg Glu Asn
          1380                1385                1390

Trp Cys Thr Ile Glu Pro Cys Pro Asp Ala Ala Ser Leu Leu Ala Ser
       1395                1400                1405

Lys Gln Ser Pro Glu Cys Glu Asn Phe Leu Asp Val Gly Leu Gly Arg
   1410                1415                1420

Glu Cys Thr Ser Lys Gln Gly Val Leu Lys Arg Glu Ser Gly Ser Asp
1425                1430                1435                1440

Ser Asp Leu Phe His Ser Pro Ser Asp Asp Met Asp Ser Ile Ile Phe
               1445                1450                1455

Pro Lys Pro Glu Glu Glu His Leu Ala Cys Asp Ile Thr Gly Ser Ser
          1460                1465                1470

Ser Ser Thr Asp Asp Thr Ala Ser Leu Asp Arg His Ser Ser His Gly
       1475                1480                1485

Ser Asp Val Ser Leu Ser Gln Ile Leu Lys Pro Asn Arg Ser Arg Asp
   1490                1495                1500

Arg Gln Ser Leu Asp Gly Phe Tyr Ser His Gly Met Gly Ala Glu Gly
1505                1510                1515                1520

Arg Glu Ser Glu Ser Glu Pro Ala Asp Pro Gly Asp Val Glu Glu Glu
               1525                1530                1535

Glu Met Asp Ser Ile Thr Glu Val Pro Ala Asn Cys Ser Val Leu Arg
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          1540                1545                1550

Ser Ser Met Arg Ser Leu Ser Pro Phe Arg Arg His Ser Trp Gly Pro
       1555                1560                1565

Gly Lys Asn Ala Ala Ser Asp Ala Glu Met Asn His Arg Ser Ser Met
   1570                1575                1580

Arg Val Leu Gly Asp Val Val Arg Arg Pro Pro Ile His Arg Arg Ser
1585                1590                1595                1600

Phe Ser Leu Glu Gly Leu Thr Gly Gly Ala Gly Val Gly Asn Lys Pro
               1605                1610                1615

Ser Ser Ser Leu Glu Val Ser Ser Ala Asn Ala Glu Glu Leu Arg His
           1620                1625                1630

Pro Phe Ser Gly Glu Glu Arg Val Asp Ser Leu Val Ser Leu Ser Glu
       1635                1640                1645

Glu Asp Leu Glu Ser Asp Gln Arg Glu His Arg Met Phe Asp Gln Gln
   1650                1655                1660

Ile Cys His Arg Ser Lys Gln Gln Gly Phe Asn Tyr Cys Thr Ser Ala
1665                1670                1675                1680

Ile Ser Ser Pro Leu Thr Lys Ser Ile Ser Leu Met Thr Ile Ser His
               1685                1690                1695

Pro Gly Leu Asp Asn Ser Arg Pro Phe His Ser Thr Phe His Asn Thr
           1700                1705                1710

Ser Ala Asn Leu Thr Glu Ser Ile Thr Glu Glu Asn Tyr Asn Phe Leu
       1715                1720                1725

Pro His Ser Pro Ser Lys Lys Asp Ser Glu Trp Lys Ser Gly Thr Lys
   1730                1735                1740

Val Ser Arg Thr Phe Ser Tyr Ile Lys Asn Lys Met Ser Ser Ser Lys
1745                1750                1755                1760

Lys Ser Lys Glu Lys Glu Lys Glu Lys Asp Lys Ile Lys Glu Lys Glu
               1765                1770                1775

Lys Asp Ser Lys Asp Lys Glu Lys Asp Lys Lys Thr Val Asn Gly His
           1780                1785                1790

Thr Phe Ser Ser Ile Pro Val Val Gly Pro Ile Ser Cys Ser Gln Cys
       1795                1800                1805

Met Lys Pro Phe Thr Asn Lys Asp Ala Tyr Thr Cys Ala Asn Cys Ser
   1810                1815                1820

Ala Phe Val His Lys Gly Cys Arg Glu Ser Leu Ala Ser Cys Ala Lys
1825                1830                1835                1840

Val Lys Met Lys Gln Pro Lys Gly Ser Leu Gln Ala His Asp Thr Ser
               1845                1850                1855

Ser Leu Pro Thr Val Ile Met Arg Asn Lys Pro Ser Gln Pro Lys Glu
           1860                1865                1870

Arg Pro Arg Ser Ala Val Leu Leu Val Asp Glu Thr Ala Thr Thr Pro
       1875                1880                1885

Ile Phe Ala Asn Arg Arg Ser Gln Gln Ser Val Ser Leu Ser Lys Ser
   1890                1895                1900

Val Ser Ile Gln Asn Ile Thr Gly Val Gly Asn Asp Glu Asn Met Ser
1905                1910                1915                1920

Asn Thr Trp Lys Phe Leu Ser His Ser Thr Asp Ser Leu Asn Lys Ile
               1925                1930                1935

Ser Lys Val Asn Glu Ser Thr Glu Ser Leu Thr Asp Glu Gly Val Gly
           1940                1945                1950
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Thr Asp Met Asn Glu Gly Gln Leu Leu Gly Asp Phe Glu Ile Glu Ser
      1955                1960                1965

Lys Gln Leu Glu Ala Glu Ser Trp Ser Arg Ile Ile Asp Ser Lys Phe
   1970                1975                1980

Leu Lys Gln Gln Lys Lys Asp Val Val Lys Arg Gln Glu Val Ile Tyr
1985                1990                1995                2000

Glu Leu Met Gln Thr Glu Phe His His Val Arg Thr Leu Lys Ile Met
              2005                2010                2015

Ser Gly Val Tyr Ser Gln Gly Met Met Ala Asp Leu Leu Phe Glu Gln
          2020                2025                2030

Gln Met Val Glu Lys Leu Phe Pro Cys Leu Asp Glu Leu Ile Ser Ile
      2035                2040                2045

His Ser Gln Phe Phe Gln Arg Ile Leu Glu Arg Lys Lys Glu Ser Leu
   2050                2055                2060

Val Asp Lys Ser Glu Lys Asn Phe Leu Ile Lys Arg Ile Gly Asp Val
2065                2070                2075                2080

Leu Val Asn Gln Phe Ser Gly Glu Asn Ala Glu Arg Leu Lys Lys Thr
              2085                2090                2095

Tyr Gly Lys Phe Cys Gly Gln His Asn Gln Ser Val Asn Tyr Phe Lys
          2100                2105                2110

Asp Leu Tyr Ala Lys Asp Lys Arg Phe Gln Ala Phe Val Lys Lys Lys
      2115                2120                2125

Met Ser Ser Ser Val Val Arg Arg Leu Gly Ile Pro Glu Cys Ile Leu
   2130                2135                2140

Leu Val Thr Gln Arg Ile Thr Lys Tyr Pro Val Leu Phe Gln Arg Ile
2145                2150                2155                2160

Leu Gln Cys Thr Lys Asp Asn Glu Val Glu Gln Glu Asp Leu Ala Gln
              2165                2170                2175

Ser Leu Ser Leu Val Lys Asp Val Ile Gly Ala Val Asp Ser Lys Val
          2180                2185                2190

Ala Ser Tyr Glu Lys Lys Val Arg Leu Asn Glu Ile Tyr Thr Lys Thr
      2195                2200                2205

Asp Ser Lys Ser Ile Met Arg Met Lys Ser Gly Gln Met Phe Ala Lys
   2210                2215                2220

Glu Asp Leu Lys Arg Lys Lys Leu Val Arg Asp Gly Ser Val Phe Leu
2225                2230                2235                2240

Lys Asn Ala Ala Gly Arg Leu Lys Glu Val Gln Ala Val Leu Leu Thr
              2245                2250                2255

Asp Ile Leu Val Phe Leu Gln Glu Lys Asp Gln Lys Tyr Ile Phe Ala
          2260                2265                2270

Ser Leu Asp Gln Lys Ser Thr Val Ile Ser Leu Lys Lys Leu Ile Val
      2275                2280                2285

Arg Glu Val Ala His Glu Glu Lys Gly Leu Phe Leu Ile Ser Met Gly
   2290                2295                2300

Met Thr Asp Pro Glu Met Val Glu Val His Ala Ser Ser Lys Glu Glu
2305                2310                2315                2320

Arg Asn Ser Trp Ile Gln Ile Ile Gln Asp Thr Ile Asn Thr Leu Asn
              2325                2330                2335

Arg Asp Glu Asp Glu Gly Ile Pro Ser Glu Asn Glu Glu Glu Lys Lys
          2340                2345                2350
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Met Leu Asp Thr Arg Ala Arg Glu Leu Lys Glu Gln Leu His Gln Lys
       2355                2360                2365

Asp Gln Lys Ile Leu Leu Leu Leu Glu Glu Lys Glu Met Ile Phe Arg
   2370                2375                2380

Asp Met Ala Glu Cys Ser Thr Pro Leu Pro Glu Asp Cys Ser Pro Thr
2385                2390                2395                2400

His Ser Pro Arg Val Leu Phe Arg Ser Asn Thr Glu Glu Ala Leu Lys
               2405                2410                2415

Gly Gly Pro Leu Met Lys Ser Ala Ile Asn Glu Val Glu Ile Leu Gln
           2420                2425                2430

Gly Leu Val Ser Gly Asn Leu Gly Gly Thr Leu Gly Pro Thr Val Ser
       2435                2440                2445

Ser Pro Ile Glu Gln Asp Val Val Gly Pro Val Ser Leu Pro Arg Arg
   2450                2455                2460

Ala Glu Thr Phe Gly Gly Phe Asp Ser His Gln Met Asn Ala Ser Lys
2465                2470                2475                2480

Gly Gly Glu Lys Glu Glu Gly Asp Asp Gly Gln Asp Leu Arg Arg Thr
               2485                2490                2495

Glu Ser Asp Ser Gly Leu Lys Lys Gly Gly Asn Ala Asn Leu Val Phe
           2500                2505                2510

Met Leu Lys Arg Asn Ser Glu Gln Val Val Gln Ser Val Val His Leu
       2515                2520                2525

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

Tyr Ile Glu Asp Gln Lys Leu Val Leu Ser Glu Arg Ala Leu Thr Arg
2545                2550                2555                2560

Ser Leu Ser Arg Pro Ser Ser Leu Ile Glu Gln Glu Lys Gln Arg Ser
               2565                2570                2575

Leu Glu Lys Gln Arg Gln Asp Leu Ala Asn Leu Gln Lys Gln Gln Ala
           2580                2585                2590

Gln Tyr Leu Glu Glu Lys Arg Arg Arg Glu Arg Glu Trp Glu Ala Arg
       2595                2600                2605

Glu Arg Glu Leu Arg Glu Arg Glu Ala Leu Leu Ala Gln Arg Glu Glu
   2610                2615                2620

Glu Val Gln Gln Gly Gln Gln Asp Leu Glu Lys Glu Arg Glu Glu Leu
2625                2630                2635                2640

Gln Gln Lys Lys Gly Thr Tyr Gln Tyr Asp Leu Glu Arg Leu Arg Ala
               2645                2650                2655

Ala Gln Lys Gln Leu Glu Arg Glu Gln Glu Gln Leu Arg Arg Glu Ala
           2660                2665                2670

Glu Arg Leu Ser Gln Arg Gln Thr Glu Arg Asp Leu Cys Gln Val Ser
       2675                2680                2685

His Pro His Thr Lys Leu Met Arg Ile Pro Ser Phe Phe Pro Ser Pro
   2690                2695                2700

Glu Glu Pro Pro Ser Pro Ser Ala Pro Ser Ile Ala Lys Ser Gly Ser
2705                2710                2715                2720

Leu Asp Ser Glu Leu Ser Val Ser Pro Lys Arg Asn Ser Ile Ser Arg
               2725                2730                2735

Thr His Lys Asp Lys Gly Pro Phe His Ile Leu Ser Ser Thr Ser Gln
           2740                2745                2750

Thr Asn Lys Gly Pro Glu Gly Gln Ser Gln Ala Pro Ala Ser Thr Ser
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      2755                2760                2765

Ala Ser Thr Arg Leu Phe Gly Leu Thr Lys Pro Lys Glu Lys Lys Glu
   2770                2775                2780

Lys Lys Lys Lys Asn Lys Thr Ser Arg Ser Gln Pro Gly Asp Gly Pro
2785                2790                2795                2800

Ala Ser Glu Val Ser Ala Glu Gly Glu Glu Ile Phe Cys
               2805                2810


<210> SEQ ID NO 17
<211> LENGTH: 2817
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Lys Leu Asn Pro Gln Gln Ala Pro Leu Tyr Gly Asp Cys Val Val
  1               5                  10                  15

Thr Val Leu Leu Ala Glu Glu Asp Lys Ala Glu Asp Asp Val Val Phe
             20                  25                  30

Tyr Leu Val Phe Leu Gly Ser Thr Leu Arg His Cys Thr Ser Thr Arg
         35                  40                  45

Lys Val Ser Ser Asp Thr Leu Glu Thr Ile Ala Pro Gly His Asp Cys
     50                  55                  60

Cys Glu Thr Val Lys Val Gln Leu Cys Ala Ser Lys Glu Gly Leu Pro
 65                  70                  75                  80

Val Phe Val Val Ala Glu Glu Asp Phe His Phe Val Gln Asp Glu Ala
                 85                  90                  95

Tyr Asp Ala Ala Gln Phe Leu Ala Thr Ser Ala Gly Asn Gln Gln Ala
            100                 105                 110

Leu Asn Phe Thr Arg Phe Leu Asp Gln Ser Gly Pro Pro Ser Gly Asp
        115                 120                 125

Val Asn Ser Leu Asp Lys Lys Leu Val Leu Ala Phe Arg His Leu Lys
    130                 135                 140

Leu Pro Thr Glu Trp Asn Val Leu Gly Thr Asp Gln Ser Leu His Asp
145                 150                 155                 160

Ala Gly Pro Arg Glu Thr Leu Met His Phe Ala Val Arg Leu Gly Leu
                165                 170                 175

Leu Arg Leu Thr Trp Phe Leu Leu Gln Lys Pro Gly Gly Arg Gly Ala
            180                 185                 190

Leu Ser Ile His Asn Gln Glu Gly Ala Thr Pro Val Ser Leu Ala Leu
        195                 200                 205

Glu Arg Gly Tyr His Lys Leu His Gln Leu Leu Thr Glu Glu Asn Ala
    210                 215                 220

Gly Glu Pro Asp Ser Trp Ser Ser Leu Ser Tyr Glu Ile Pro Tyr Gly
225                 230                 235                 240

Asp Cys Ser Val Arg His His Arg Glu Leu Asp Ile Tyr Thr Leu Thr
                245                 250                 255

Ser Glu Ser Asp Ser His His Glu His Pro Phe Pro Gly Asp Gly Cys
            260                 265                 270

Thr Gly Pro Ile Phe Lys Leu Met Asn Ile Gln Gln Gln Leu Met Lys
        275                 280                 285

Thr Asn Leu Lys Gln Met Asp Ser Leu Met Pro Leu Met Met Thr Ala
    290                 295                 300
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Gln Asp Pro Ser Ser Ala Pro Glu Thr Asp Gly Gln Phe Leu Pro Cys
305                 310                 315                 320

Ala Pro Glu Pro Thr Asp Pro Gln Arg Leu Ser Ser Ser Glu Glu Thr
                325                 330                 335

Glu Ser Thr Gln Cys Cys Pro Gly Ser Pro Val Ala Gln Thr Glu Ser
            340                 345                 350

Pro Cys Asp Leu Ser Ser Ile Val Glu Glu Glu Asn Thr Asp Arg Ser
        355                 360                 365

Cys Arg Lys Lys Asn Lys Gly Val Glu Arg Lys Gly Glu Glu Val Glu
    370                 375                 380

Pro Ala Pro Ile Val Asp Ser Gly Thr Val Ser Asp Gln Asp Ser Cys
385                 390                 395                 400

Leu Gln Ser Leu Pro Asp Cys Gly Val Lys Gly Thr Glu Gly Leu Ser
                405                 410                 415

Ser Cys Gly Asn Arg Asn Glu Glu Thr Gly Thr Lys Ser Ser Gly Met
            420                 425                 430

Pro Thr Asp Gln Glu Ser Leu Ser Ser Gly Asp Ala Val Leu Gln Arg
        435                 440                 445

Asp Leu Val Met Glu Pro Gly Thr Ala Gln Tyr Ser Ser Gly Gly Glu
    450                 455                 460

Leu Gly Gly Ile Ser Thr Thr Asn Val Ser Thr Pro Asp Thr Ala Gly
465                 470                 475                 480

Glu Met Glu His Gly Leu Met Asn Pro Asp Ala Thr Val Trp Lys Asn
                485                 490                 495

Val Leu Gln Gly Gly Glu Ser Thr Lys Glu Arg Phe Glu Asn Ser Asn
            500                 505                 510

Ile Gly Thr Ala Gly Ala Ser Asp Val His Val Thr Ser Lys Pro Val
        515                 520                 525

Asp Lys Ile Ser Val Pro Asn Cys Ala Pro Ala Ala Ser Ser Leu Asp
    530                 535                 540

Gly Asn Lys Pro Ala Glu Ser Ser Leu Ala Phe Ser Asn Glu Glu Thr
545                 550                 555                 560

Ser Thr Glu Lys Thr Ala Glu Thr Glu Thr Ser Arg Ser Arg Glu Glu
                565                 570                 575

Ser Ala Asp Ala Pro Val Asp Gln Asn Ser Val Val Ile Pro Ala Ala
            580                 585                 590

Ala Lys Asp Lys Ile Ser Asp Gly Leu Glu Pro Tyr Thr Leu Leu Ala
        595                 600                 605

Ala Gly Ile Gly Glu Ala Met Ser Pro Ser Asp Leu Ala Leu Leu Gly
    610                 615                 620

Leu Glu Glu Asp Val Met Pro His Gln Asn Ser Glu Thr Asn Ser Ser
625                 630                 635                 640

His Ala Gln Ser Gln Lys Gly Lys Ser Ser Pro Ile Cys Ser Thr Thr
                645                 650                 655

Gly Asp Asp Lys Leu Cys Ala Asp Ser Ala Cys Gln Gln Asn Thr Val
            660                 665                 670

Thr Ser Ser Gly Asp Leu Val Ala Lys Leu Cys Asp Asn Ile Val Ser
        675                 680                 685

Glu Ser Glu Ser Thr Thr Ala Arg Gln Pro Ser Ser Gln Asp Pro Pro
    690                 695                 700

Asp Ala Ser His Cys Glu Asp Pro Gln Ala His Thr Val Thr Ser Asp
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705                 710                 715                 720

Pro Val Arg Asp Thr Gln Glu Arg Ala Asp Phe Cys Pro Phe Lys Val
                725                 730                 735

Val Asp Asn Lys Gly Gln Arg Lys Asp Val Lys Leu Asp Lys Pro Leu
            740                 745                 750

Thr Asn Met Leu Glu Val Val Ser His Pro His Pro Val Val Pro Lys
        755                 760                 765

Met Glu Lys Glu Leu Val Pro Asp Gln Ala Val Ile Ser Asp Ser Thr
    770                 775                 780

Phe Ser Leu Ala Asn Ser Pro Gly Ser Glu Ser Val Thr Lys Asp Asp
785                 790                 795                 800

Ala Leu Ser Phe Val Pro Ser Gln Lys Glu Lys Gly Thr Ala Thr Pro
                805                 810                 815

Glu Leu His Thr Ala Thr Asp Tyr Arg Asp Gly Pro Asp Gly Asn Ser
            820                 825                 830

Asn Glu Pro Asp Thr Arg Pro Leu Glu Asp Arg Ala Val Gly Leu Ser
        835                 840                 845

Thr Ser Ser Thr Ala Ala Glu Leu Gln His Gly Met Gly Asn Thr Ser
    850                 855                 860

Leu Thr Gly Leu Gly Gly Glu His Glu Gly Pro Ala Pro Pro Ala Ile
865                 870                 875                 880

Pro Glu Ala Leu Asn Ile Lys Gly Asn Thr Asp Ser Ser Leu Gln Ser
                885                 890                 895

Val Gly Lys Ala Thr Leu Ala Leu Asp Ser Val Leu Thr Glu Glu Gly
            900                 905                 910

Lys Leu Leu Val Val Ser Glu Ser Ser Ala Ala Gln Glu Gln Asp Lys
        915                 920                 925

Asp Lys Ala Val Thr Cys Ser Ser Ile Lys Glu Asn Ala Leu Ser Ser
    930                 935                 940

Gly Thr Leu Gln Glu Glu Gln Arg Thr Pro Pro Pro Gly Gln Asp Thr
945                 950                 955                 960

Gln Gln Phe His Glu Lys Ser Ile Ser Ala Asp Cys Ala Lys Asp Lys
                965                 970                 975

Ala Leu Gln Leu Ser Asn Ser Pro Gly Ala Ser Ser Ala Phe Leu Lys
            980                 985                 990

Ala Glu Thr Glu His Asn Lys Glu Val Ala Pro Gln Val Ser Leu Leu
        995                1000                1005

Thr Gln Gly Gly Ala Ala Gln Ser Leu Val Pro Pro Gly Ala Ser Leu
   1010                1015                1020

Ala Thr Glu Ser Arg Gln Glu Ala Leu Gly Ala Glu His Asn Ser Ser
1025                1030                1035                1040

Ala Leu Leu Pro Cys Leu Leu Pro Asp Gly Ser Asp Gly Ser Asp Ala
                1045                1050                1055

Leu Asn Cys Ser Gln Pro Ser Pro Leu Asp Val Gly Val Lys Asn Thr
            1060                1065                1070

Gln Ser Gln Gly Lys Thr Ser Ala Cys Glu Val Ser Gly Asp Val Thr
        1075                1080                1085

Val Asp Val Thr Gly Val Asn Ala Leu Gln Gly Met Ala Glu Pro Arg
   1090                1095                1100

Arg Glu Asn Ile Ser His Asn Thr Gln Asp Ile Leu Ile Pro Asn Val
1105                1110                1115                1120
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Leu Leu Ser Gln Glu Lys Asn Ala Val Leu Gly Leu Pro Val Ala Leu
              1125                1130                1135

Gln Asp Lys Ala Val Thr Asp Pro Gln Gly Val Gly Thr Pro Glu Met
          1140                1145                1150

Ile Pro Leu Asp Trp Glu Lys Gly Lys Leu Glu Gly Ala Asp His Ser
       1155                1160                1165

Cys Thr Met Gly Asp Ala Glu Glu Ala Gln Ile Asp Asp Glu Ala His
   1170                1175                1180

Pro Val Leu Leu Gln Pro Val Ala Lys Glu Leu Pro Thr Asp Met Glu
1185                1190                1195                1200

Leu Ser Ala His Asp Asp Gly Ala Pro Ala Gly Val Arg Glu Val Met
              1205                1210                1215

Arg Ala Pro Pro Ser Gly Arg Glu Arg Ser Thr Pro Ser Leu Pro Cys
          1220                1225                1230

Met Val Ser Ala Gln Asp Ala Pro Leu Pro Lys Gly Ala Asp Leu Ile
       1235                1240                1245

Glu Glu Ala Ala Ser Arg Ile Val Asp Ala Val Ile Glu Gln Val Lys
   1250                1255                1260

Ala Ala Gly Ala Leu Leu Thr Glu Gly Glu Ala Cys His Met Ser Leu
1265                1270                1275                1280

Ser Ser Pro Glu Leu Gly Pro Leu Thr Lys Gly Leu Glu Ser Ala Phe
              1285                1290                1295

Thr Glu Lys Val Ser Thr Phe Pro Pro Gly Glu Ser Leu Pro Met Gly
          1300                1305                1310

Ser Thr Pro Glu Glu Ala Thr Gly Ser Leu Ala Gly Cys Phe Ala Gly
       1315                1320                1325

Arg Glu Glu Pro Glu Lys Ile Ile Leu Pro Val Gln Gly Pro Glu Pro
   1330                1335                1340

Ala Ala Glu Met Pro Asp Val Lys Ala Glu Asp Glu Val Asp Phe Arg
1345                1350                1355                1360

Ala Ser Ser Ile Ser Glu Glu Val Ala Val Gly Ser Ile Ala Ala Thr
              1365                1370                1375

Leu Lys Met Lys Gln Gly Pro Met Thr Gln Ala Ile Asn Arg Glu Asn
          1380                1385                1390

Trp Cys Thr Ile Glu Pro Cys Pro Asp Ala Ala Ser Leu Leu Ala Ser
       1395                1400                1405

Lys Gln Ser Pro Glu Cys Glu Asn Phe Leu Asp Val Gly Leu Gly Arg
   1410                1415                1420

Glu Cys Thr Ser Lys Gln Gly Val Leu Lys Arg Glu Ser Gly Ser Asp
1425                1430                1435                1440

Ser Asp Leu Phe His Ser Pro Ser Asp Asp Met Asp Ser Ile Ile Phe
              1445                1450                1455

Pro Lys Pro Glu Glu Glu His Leu Ala Cys Asp Ile Thr Gly Ser Ser
          1460                1465                1470

Ser Ser Thr Asp Asp Thr Ala Ser Leu Asp Arg His Ser Ser His Gly
       1475                1480                1485

Ser Asp Val Ser Leu Ser Gln Ile Leu Lys Pro Asn Arg Ser Arg Asp
   1490                1495                1500

Arg Gln Ser Leu Asp Gly Phe Tyr Ser His Gly Met Gly Ala Glu Gly
1505                1510                1515                1520
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Arg Glu Ser Glu Ser Glu Pro Ala Asp Pro Gly Asp Val Glu Glu Glu
             1525                1530                1535

Glu Met Asp Ser Ile Thr Glu Val Pro Ala Asn Cys Ser Val Leu Arg
          1540                1545                1550

Ser Ser Met Arg Ser Leu Ser Pro Phe Arg Arg His Ser Trp Gly Pro
       1555                1560                1565

Gly Lys Asn Ala Ala Ser Asp Ala Glu Met Asn His Arg Ser Met Ser
   1570                1575                1580

Trp Cys Pro Ser Gly Val Gln Tyr Ser Ala Gly Leu Ser Ala Asp Phe
1585                1590                1595                1600

Asn Tyr Arg Ser Phe Ser Leu Glu Gly Leu Thr Gly Gly Ala Gly Val
             1605                1610                1615

Gly Asn Lys Pro Ser Ser Ser Leu Glu Val Ser Ser Ala Asn Ala Glu
          1620                1625                1630

Glu Leu Arg His Pro Phe Ser Gly Glu Glu Arg Val Asp Ser Leu Val
       1635                1640                1645

Ser Leu Ser Glu Glu Asp Leu Glu Ser Asp Gln Arg Glu His Arg Met
   1650                1655                1660

Phe Asp Gln Gln Ile Cys His Arg Ser Lys Gln Gln Gly Phe Asn Tyr
1665                1670                1675                1680

Cys Thr Ser Ala Ile Ser Ser Pro Leu Thr Lys Ser Ile Ser Leu Met
             1685                1690                1695

Thr Ile Ser His Pro Gly Leu Asp Asn Ser Arg Pro Phe His Ser Thr
          1700                1705                1710

Phe His Asn Thr Ser Ala Asn Leu Thr Glu Ser Ile Thr Glu Glu Asn
       1715                1720                1725

Tyr Asn Phe Leu Pro His Ser Pro Ser Lys Lys Asp Ser Glu Trp Lys
   1730                1735                1740

Ser Gly Thr Lys Val Ser Arg Thr Phe Ser Tyr Ile Lys Asn Lys Met
1745                1750                1755                1760

Ser Ser Ser Lys Lys Ser Lys Glu Lys Glu Lys Glu Lys Asp Lys Ile
             1765                1770                1775

Lys Glu Lys Glu Lys Asp Ser Lys Asp Lys Glu Lys Asp Lys Lys Thr
          1780                1785                1790

Val Asn Gly His Thr Phe Ser Ser Ile Pro Val Val Gly Pro Ile Ser
       1795                1800                1805

Cys Ser Gln Cys Met Lys Pro Phe Thr Asn Lys Asp Ala Tyr Thr Cys
   1810                1815                1820

Ala Asn Cys Ser Ala Phe Val His Lys Gly Cys Arg Glu Ser Leu Ala
1825                1830                1835                1840

Ser Cys Ala Lys Val Lys Met Lys Gln Pro Lys Gly Ser Leu Gln Ala
             1845                1850                1855

His Asp Thr Ser Ser Leu Pro Thr Val Ile Met Arg Asn Lys Pro Ser
          1860                1865                1870

Gln Pro Lys Glu Arg Pro Arg Ser Ala Val Leu Leu Val Asp Glu Thr
       1875                1880                1885

Ala Thr Thr Pro Ile Phe Ala Asn Arg Arg Ser Gln Gln Ser Val Ser
   1890                1895                1900

Leu Ser Lys Ser Val Ser Ile Gln Asn Ile Thr Gly Val Gly Asn Asp
1905                1910                1915                1920

Glu Asn Met Ser Asn Thr Trp Lys Phe Leu Ser His Ser Thr Asp Ser
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             1925                1930                1935

Leu Asn Lys Ile Ser Lys Val Asn Glu Ser Thr Glu Ser Leu Thr Asp
          1940                1945                1950

Glu Gly Val Gly Thr Asp Met Asn Glu Gly Gln Leu Leu Gly Asp Phe
       1955                1960                1965

Glu Ile Glu Ser Lys Gln Leu Glu Ala Glu Ser Trp Ser Arg Ile Ile
   1970                1975                1980

Asp Ser Lys Phe Leu Lys Gln Gln Lys Lys Asp Val Val Lys Arg Gln
1985                1990                1995                2000

Glu Val Ile Tyr Glu Leu Met Gln Thr Glu Phe His His Val Arg Thr
             2005                2010                2015

Leu Lys Ile Met Ser Gly Val Tyr Ser Gln Gly Met Met Ala Asp Leu
          2020                2025                2030

Leu Phe Glu Gln Gln Met Val Glu Lys Leu Phe Pro Cys Leu Asp Glu
       2035                2040                2045

Leu Ile Ser Ile His Ser Gln Phe Phe Gln Arg Ile Leu Glu Arg Lys
   2050                2055                2060

Lys Glu Ser Leu Val Asp Lys Ser Glu Lys Asn Phe Leu Ile Lys Arg
2065                2070                2075                2080

Ile Gly Asp Val Leu Val Asn Gln Phe Ser Gly Glu Asn Ala Glu Arg
             2085                2090                2095

Leu Lys Lys Thr Tyr Gly Lys Phe Cys Gly Gln His Asn Gln Ser Val
          2100                2105                2110

Asn Tyr Phe Lys Asp Leu Tyr Ala Lys Asp Lys Arg Phe Gln Ala Phe
       2115                2120                2125

Val Lys Lys Lys Met Ser Ser Ser Val Val Arg Arg Leu Gly Ile Pro
   2130                2135                2140

Glu Cys Ile Leu Leu Val Thr Gln Arg Ile Thr Lys Tyr Pro Val Leu
2145                2150                2155                2160

Phe Gln Arg Ile Leu Gln Cys Thr Lys Asp Asn Glu Val Glu Gln Glu
             2165                2170                2175

Asp Leu Ala Gln Ser Leu Ser Leu Val Lys Asp Val Ile Gly Ala Val
          2180                2185                2190

Asp Ser Lys Val Ala Ser Tyr Glu Lys Lys Val Arg Leu Asn Glu Ile
       2195                2200                2205

Tyr Thr Lys Thr Asp Ser Lys Ser Ile Met Arg Met Lys Ser Gly Gln
   2210                2215                2220

Met Phe Ala Lys Glu Asp Leu Lys Arg Lys Lys Leu Val Arg Asp Gly
2225                2230                2235                2240

Ser Val Phe Leu Lys Asn Ala Ala Gly Arg Leu Lys Glu Val Gln Ala
             2245                2250                2255

Val Leu Leu Thr Asp Ile Leu Val Phe Leu Gln Glu Lys Asp Gln Lys
          2260                2265                2270

Tyr Ile Phe Ala Ser Leu Asp Gln Lys Ser Thr Val Ile Ser Leu Lys
       2275                2280                2285

Lys Leu Ile Val Arg Glu Val Ala His Glu Glu Lys Gly Leu Phe Leu
   2290                2295                2300

Ile Ser Met Gly Met Thr Asp Pro Glu Met Val Glu Val His Ala Ser
2305                2310                2315                2320

Ser Lys Glu Glu Arg Asn Ser Trp Ile Gln Ile Ile Gln Asp Thr Ile
             2325                2330                2335
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Asn Thr Leu Asn Arg Asp Glu Asp Glu Gly Ile Pro Ser Glu Asn Glu
          2340                2345                2350

Glu Glu Lys Lys Met Leu Asp Thr Arg Ala Arg Glu Leu Lys Glu Gln
       2355                2360                2365

Leu His Gln Lys Asp Gln Lys Ile Leu Leu Leu Leu Glu Glu Lys Glu
   2370                2375                2380

Met Ile Phe Arg Asp Met Ala Glu Cys Ser Thr Pro Leu Pro Glu Asp
2385                2390                2395                2400

Cys Ser Pro Thr His Ser Pro Arg Val Leu Phe Arg Ser Asn Thr Glu
               2405                2410                2415

Glu Ala Leu Lys Gly Gly Pro Leu Met Lys Ser Ala Ile Asn Glu Val
          2420                2425                2430

Glu Ile Leu Gln Gly Leu Val Ser Gly Asn Leu Gly Gly Thr Leu Gly
       2435                2440                2445

Pro Thr Val Ser Ser Pro Ile Glu Gln Asp Val Val Gly Pro Val Ser
   2450                2455                2460

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

Asn Ala Ser Lys Gly Gly Glu Lys Glu Glu Gly Asp Asp Gly Gln Asp
               2485                2490                2495

Leu Arg Arg Thr Glu Ser Asp Ser Gly Leu Lys Lys Gly Gly Asn Ala
          2500                2505                2510

Asn Leu Val Phe Met Leu Lys Arg Asn Ser Glu Gln Val Val Gln Ser
       2515                2520                2525

Val Val His Leu Tyr Glu Leu Leu Ser Ala Leu Gln Gly Val Val Leu
   2530                2535                2540

Gln Gln Asp Ser Tyr Ile Glu Asp Gln Lys Leu Val Leu Ser Glu Arg
2545                2550                2555                2560

Ala Leu Thr Arg Ser Leu Ser Arg Pro Ser Ser Leu Ile Glu Gln Glu
               2565                2570                2575

Lys Gln Arg Ser Leu Glu Lys Gln Arg Gln Asp Leu Ala Asn Leu Gln
          2580                2585                2590

Lys Gln Gln Ala Gln Tyr Leu Glu Glu Lys Arg Arg Arg Glu Arg Glu
       2595                2600                2605

Trp Glu Ala Arg Glu Arg Glu Leu Arg Glu Arg Glu Ala Leu Leu Ala
   2610                2615                2620

Gln Arg Glu Glu Glu Val Gln Gln Gly Gln Gln Asp Leu Glu Lys Glu
2625                2630                2635                2640

Arg Glu Glu Leu Gln Gln Lys Lys Gly Thr Tyr Gln Tyr Asp Leu Glu
               2645                2650                2655

Arg Leu Arg Ala Ala Gln Lys Gln Leu Glu Arg Glu Gln Glu Gln Leu
          2660                2665                2670

Arg Arg Glu Ala Glu Arg Leu Ser Gln Arg Gln Thr Glu Arg Asp Leu
       2675                2680                2685

Cys Gln Val Ser His Pro His Thr Lys Leu Met Arg Ile Pro Ser Phe
   2690                2695                2700

Phe Pro Ser Pro Glu Glu Pro Pro Ser Pro Ser Ala Pro Ser Ile Ala
2705                2710                2715                2720

Lys Ser Gly Ser Leu Asp Ser Glu Leu Ser Val Ser Pro Lys Arg Asn
               2725                2730                2735
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Ser Ile Ser Arg Thr His Lys Asp Lys Gly Pro Phe His Ile Leu Ser
          2740                2745                2750

Ser Thr Ser Gln Thr Asn Lys Gly Pro Glu Gly Gln Ser Gln Ala Pro
       2755                2760                2765

Ala Ser Thr Ser Ala Ser Thr Arg Leu Phe Gly Leu Thr Lys Pro Lys
   2770                2775                2780

Glu Lys Lys Glu Lys Lys Lys Lys Asn Lys Thr Ser Arg Ser Gln Pro
2785                2790                2795                2800

Gly Asp Gly Pro Ala Ser Glu Val Ser Ala Glu Gly Glu Glu Ile Phe
               2805                2810                2815

Cys
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<210> SEQ ID NO 18
<211> LENGTH: 1058
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

```
Met Ser Ser Ser Lys Lys Ser Lys Glu Lys Glu Lys Glu Lys Asp Lys
  1               5                  10                  15

Ile Lys Glu Lys Glu Lys Asp Ser Lys Asp Lys Glu Lys Asp Lys Lys
             20                  25                  30

Thr Val Asn Gly His Thr Phe Ser Ser Ile Pro Val Val Gly Pro Ile
         35                  40                  45

Ser Cys Ser Gln Cys Met Lys Pro Phe Thr Asn Lys Asp Ala Tyr Thr
     50                  55                  60

Cys Ala Asn Cys Ser Ala Phe Val His Lys Gly Cys Arg Glu Ser Leu
 65                  70                  75                  80

Ala Ser Cys Ala Lys Val Lys Met Lys Gln Pro Lys Gly Ser Leu Gln
                 85                  90                  95

Ala His Asp Thr Ser Ser Leu Pro Thr Val Ile Met Arg Asn Lys Pro
            100                 105                 110

Ser Gln Pro Lys Glu Arg Pro Arg Ser Ala Val Leu Leu Val Asp Glu
        115                 120                 125

Thr Ala Thr Thr Pro Ile Phe Ala Asn Arg Arg Ser Gln Gln Ser Val
    130                 135                 140

Ser Leu Ser Lys Ser Val Ser Ile Gln Asn Ile Thr Gly Val Gly Asn
145                 150                 155                 160

Asp Glu Asn Met Ser Asn Thr Trp Lys Phe Leu Ser His Ser Thr Asp
                165                 170                 175

Ser Leu Asn Lys Ile Ser Lys Val Asn Glu Ser Thr Glu Ser Leu Thr
            180                 185                 190

Asp Glu Gly Val Gly Thr Asp Met Asn Glu Gly Gln Leu Leu Gly Asp
        195                 200                 205

Phe Glu Ile Glu Ser Lys Gln Leu Glu Ala Glu Ser Trp Ser Arg Ile
    210                 215                 220

Ile Asp Ser Lys Phe Leu Lys Gln Gln Lys Lys Asp Val Val Lys Arg
225                 230                 235                 240

Gln Glu Val Ile Tyr Glu Leu Met Gln Thr Glu Phe His His Val Arg
                245                 250                 255

Thr Leu Lys Ile Met Ser Gly Val Tyr Ser Gln Gly Met Met Ala Asp
            260                 265                 270
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Leu Leu Phe Glu Gln Gln Met Val Glu Lys Leu Phe Pro Cys Leu Asp
        275                 280                 285

Glu Leu Ile Ser Ile His Ser Gln Phe Phe Gln Arg Ile Leu Glu Arg
    290                 295                 300

Lys Lys Glu Ser Leu Val Asp Lys Ser Glu Lys Asn Phe Leu Ile Lys
305                 310                 315                 320

Arg Ile Gly Asp Val Leu Val Asn Gln Phe Ser Gly Glu Asn Ala Glu
                325                 330                 335

Arg Leu Lys Lys Thr Tyr Gly Lys Phe Cys Gly Gln His Asn Gln Ser
            340                 345                 350

Val Asn Tyr Phe Lys Asp Leu Tyr Ala Lys Asp Lys Arg Phe Gln Ala
        355                 360                 365

Phe Val Lys Lys Lys Met Ser Ser Ser Val Val Arg Arg Leu Gly Ile
    370                 375                 380

Pro Glu Cys Ile Leu Leu Val Thr Gln Arg Ile Thr Lys Tyr Pro Val
385                 390                 395                 400

Leu Phe Gln Arg Ile Leu Gln Cys Thr Lys Asp Asn Glu Val Glu Gln
                405                 410                 415

Glu Asp Leu Ala Gln Ser Leu Ser Leu Val Lys Asp Val Ile Gly Ala
            420                 425                 430

Val Asp Ser Lys Val Ala Ser Tyr Glu Lys Lys Val Arg Leu Asn Glu
        435                 440                 445

Ile Tyr Thr Lys Thr Asp Ser Lys Ser Ile Met Arg Met Lys Ser Gly
    450                 455                 460

Gln Met Phe Ala Lys Glu Asp Leu Lys Arg Lys Lys Leu Val Arg Asp
465                 470                 475                 480

Gly Ser Val Phe Leu Lys Asn Ala Ala Gly Arg Leu Lys Glu Val Gln
                485                 490                 495

Ala Val Leu Leu Thr Asp Ile Leu Val Phe Leu Gln Glu Lys Asp Gln
            500                 505                 510

Lys Tyr Ile Phe Ala Ser Leu Asp Gln Lys Ser Thr Val Ile Ser Leu
        515                 520                 525

Lys Lys Leu Ile Val Arg Glu Val Ala His Glu Glu Lys Gly Leu Phe
    530                 535                 540

Leu Ile Ser Met Gly Met Thr Asp Pro Glu Met Val Glu Val His Ala
545                 550                 555                 560

Ser Ser Lys Glu Glu Arg Asn Ser Trp Ile Gln Ile Ile Gln Asp Thr
                565                 570                 575

Ile Asn Thr Leu Asn Arg Asp Glu Asp Glu Gly Ile Pro Ser Glu Asn
            580                 585                 590

Glu Glu Glu Lys Lys Met Leu Asp Thr Arg Ala Arg Glu Leu Lys Glu
        595                 600                 605

Gln Leu His Gln Lys Asp Gln Lys Ile Leu Leu Leu Leu Glu Glu Lys
    610                 615                 620

Glu Met Ile Phe Arg Asp Met Ala Glu Cys Ser Thr Pro Leu Pro Glu
625                 630                 635                 640

Asp Cys Ser Pro Thr His Ser Pro Arg Val Leu Phe Arg Ser Asn Thr
                645                 650                 655

Glu Glu Ala Leu Lys Gly Gly Pro Leu Met Lys Ser Ala Ile Asn Glu
            660                 665                 670

Val Glu Ile Leu Gln Gly Leu Val Ser Gly Asn Leu Gly Gly Thr Leu
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        675                 680                 685

Gly Pro Thr Val Ser Ser Pro Ile Glu Gln Asp Val Val Gly Pro Val
    690                 695                 700

Ser Leu Pro Arg Arg Ala Glu Thr Phe Gly Gly Phe Asp Ser His Gln
705                 710                 715                 720

Met Asn Ala Ser Lys Gly Gly Glu Lys Glu Glu Gly Asp Asp Gly Gln
                725                 730                 735

Asp Leu Arg Arg Thr Glu Ser Asp Ser Gly Leu Lys Lys Gly Gly Asn
            740                 745                 750

Ala Asn Leu Val Phe Met Leu Lys Arg Asn Ser Glu Gln Val Val Gln
        755                 760                 765

Ser Val Val His Leu Tyr Glu Leu Leu Ser Ala Leu Gln Gly Val Val
    770                 775                 780

Leu Gln Gln Asp Ser Tyr Ile Glu Asp Gln Lys Leu Val Leu Ser Glu
785                 790                 795                 800

Arg Ala Leu Thr Arg Ser Leu Ser Arg Pro Ser Ser Leu Ile Glu Gln
                805                 810                 815

Glu Lys Gln Arg Ser Leu Glu Lys Gln Arg Gln Asp Leu Ala Asn Leu
            820                 825                 830

Gln Lys Gln Gln Ala Gln Tyr Leu Glu Glu Lys Arg Arg Arg Glu Arg
        835                 840                 845

Glu Trp Glu Ala Arg Glu Arg Glu Leu Arg Glu Arg Glu Ala Leu Leu
    850                 855                 860

Ala Gln Arg Glu Glu Glu Val Gln Gln Gly Gln Gln Asp Leu Glu Lys
865                 870                 875                 880

Glu Arg Glu Glu Leu Gln Gln Lys Lys Gly Thr Tyr Gln Tyr Asp Leu
                885                 890                 895

Glu Arg Leu Arg Ala Ala Gln Lys Gln Leu Glu Arg Glu Gln Glu Gln
            900                 905                 910

Leu Arg Arg Glu Ala Glu Arg Leu Ser Gln Arg Gln Thr Glu Arg Asp
        915                 920                 925

Leu Cys Gln Val Ser His Pro His Thr Lys Leu Met Arg Ile Pro Ser
    930                 935                 940

Phe Phe Pro Ser Pro Glu Glu Pro Pro Ser Pro Ser Ala Pro Ser Ile
945                 950                 955                 960

Ala Lys Ser Gly Ser Leu Asp Ser Glu Leu Ser Val Ser Pro Lys Arg
                965                 970                 975

Asn Ser Ile Ser Arg Thr His Lys Asp Lys Gly Pro Phe His Ile Leu
            980                 985                 990

Ser Ser Thr Ser Gln Thr Asn Lys Gly Pro Glu Gly Gln Ser Gln Ala
        995                1000                1005

Pro Ala Ser Thr Ser Ala Ser Thr Arg Leu Phe Gly Leu Thr Lys Pro
   1010                1015                1020

Lys Glu Lys Lys Glu Lys Lys Lys Lys Asn Lys Thr Ser Arg Ser Gln
1025                1030                1035                1040

Pro Gly Asp Gly Pro Ala Ser Glu Val Ser Ala Glu Gly Glu Glu Ile
                1045                1050                1055

Phe Cys
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<210> SEQ ID NO 19
<211> LENGTH: 1105

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

```
Met Ser Ala Lys Ala Ile Ser Glu Gln Thr Gly Lys Glu Leu Leu Tyr
  1               5                  10                  15

Lys Phe Ile Cys Thr Thr Ser Ala Ile Gln Asn Arg Phe Lys Tyr Ala
             20                  25                  30

Arg Val Thr Pro Asp Thr Asp Trp Ala Arg Leu Leu Gln Asp His Pro
         35                  40                  45

Trp Leu Leu Ser Gln Asn Leu Val Val Lys Pro Asp Gln Leu Ile Lys
     50                  55                  60

Arg Arg Gly Lys Leu Gly Leu Val Gly Val Asp Leu Thr Leu Asp Gly
 65                  70                  75                  80

Val Lys Ser Trp Leu Lys Pro Arg Leu Gly Gln Glu Ala Thr Val Gly
                 85                  90                  95

Lys Ala Thr Gly Phe Leu Lys Asn Phe Leu Ile Glu Pro Phe Ala Pro
            100                 105                 110

His Ser Gln Ala Glu Glu Phe Tyr Val Cys Ile Tyr Ala Thr Arg Glu
        115                 120                 125

Gly Asp Tyr Val Leu Phe His His Glu Gly Gly Val Asp Val Gly Asp
    130                 135                 140

Val Asp Ala Lys Ala Gln Lys Leu Leu Val Gly Val Asp Glu Lys Leu
145                 150                 155                 160

Asn Pro Glu Asp Ile Lys Lys His Leu Leu Val His Ala Pro Asp Asp
                165                 170                 175

Lys Lys Glu Ile Leu Ala Ser Phe Ile Ser Gly Leu Phe Asn Phe Tyr
            180                 185                 190

Glu Asp Leu Tyr Phe Thr Tyr Leu Glu Ile Asn Pro Leu Val Val Thr
        195                 200                 205

Lys Asp Gly Val Tyr Val Leu Asp Leu Ala Ala Lys Val Asp Ala Thr
    210                 215                 220

Ala Asp Tyr Ile Cys Lys Val Lys Trp Gly Asp Ile Glu Phe Pro Pro
225                 230                 235                 240

Pro Phe Gly Arg Val Ala Tyr Pro Glu Glu Ala Tyr Ile Ala Asp Leu
                245                 250                 255

Asp Ala Lys Ser Gly Ala Ser Leu Lys Leu Thr Leu Leu Asn Pro Lys
            260                 265                 270

Gly Arg Ile Trp Thr Met Val Ala Gly Gly Gly Ala Ser Val Val Tyr
        275                 280                 285

Ser Asp Thr Ile Cys Asp Leu Gly Gly Val Asn Glu Leu Ala Asn Tyr
    290                 295                 300

Gly Glu Tyr Ser Gly Ala Pro Ser Glu Gln Gln Thr Tyr Asp Tyr Ala
305                 310                 315                 320

Lys Thr Ile Leu Ser Leu Met Thr Arg Glu Lys His Pro Asp Gly Lys
                325                 330                 335

Ile Leu Ile Ile Gly Gly Ser Ile Ala Asn Phe Thr Asn Val Ala Ala
            340                 345                 350

Thr Phe Lys Gly Ile Val Arg Ala Ile Arg Asp Tyr Gln Gly Pro Leu
        355                 360                 365

Lys Glu His Glu Val Thr Ile Phe Val Arg Arg Gly Gly Pro Asn Tyr
    370                 375                 380
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Gln Glu Gly Leu Arg Val Met Gly Glu Val Gly Lys Thr Thr Gly Ile
385                 390                 395                 400

Pro Ile His Val Phe Gly Thr Glu Thr His Met Thr Ala Ile Val Gly
                405                 410                 415

Met Ala Trp Ala Pro Ala Ile Pro Asn Gln Pro Pro Thr Ala Ala His
            420                 425                 430

Thr Ala Asn Phe Leu Leu Asn Ala Gln Arg Glu Thr Ser Thr Pro Ala
        435                 440                 445

Pro Ser Arg Thr Ala Ser Phe Tyr Glu Ser Met Val Asp Glu Val Arg
    450                 455                 460

Ala Asp Glu Val Ala Pro Ala Lys Lys Ala Lys Pro Ala Met Pro Gln
465                 470                 475                 480

Asp Ser Val Pro Ser Pro Arg Ser Leu Gln Gly Lys Ser Thr Thr Leu
                485                 490                 495

Phe Ser Arg His Thr Lys Ala Ile Val Trp Gly Met Gln Thr Arg Ala
            500                 505                 510

Val Gln Gly Met Leu Asp Phe Asp Tyr Val Cys Ser Arg Asp Glu Pro
        515                 520                 525

Ser Val Ala Ala Met Val Tyr Pro Phe Thr Gly Asp His Lys Gln Lys
    530                 535                 540

Phe Tyr Trp Gly His Lys Glu Ile Leu Ile Pro Val Phe Lys Asn Met
545                 550                 555                 560

Ala Asp Ala Met Arg Lys His Pro Glu Val Asp Val Leu Ile Asn Phe
                565                 570                 575

Ala Ser Leu Arg Ser Ala Tyr Asp Ser Thr Met Glu Thr Met Asn Tyr
            580                 585                 590

Ala Gln Ile Arg Thr Ile Ala Ile Ile Ala Glu Gly Ile Pro Glu Ala
        595                 600                 605

Leu Thr Arg Lys Leu Ile Lys Lys Ala Asp Gln Lys Gly Val Thr Ile
    610                 615                 620

Ile Gly Pro Ala Thr Val Gly Gly Ile Lys Pro Gly Cys Phe Lys Ile
625                 630                 635                 640

Gly Asn Thr Gly Gly Met Leu Asp Asn Ile Leu Ala Ser Lys Leu Tyr
                645                 650                 655

Pro Gln Ala Ala Val Ala Tyr Val Ser Arg Ser Gly Gly Met Ser Asn
            660                 665                 670

Glu Leu Asn Asn Ile Ile Ser Arg Thr Thr Asp Gly Val Tyr Glu Gly
        675                 680                 685

Val Ala Ile Gly Gly Asp Arg Tyr Pro Gly Ser Thr Phe Met Asp His
    690                 695                 700

Val Leu Arg Tyr Gln Asp Thr Pro Gly Val Lys Met Ile Val Val Leu
705                 710                 715                 720

Gly Glu Ile Gly Gly Thr Glu Glu Tyr Lys Ile Ser Arg Gly Ile Lys
                725                 730                 735

Glu Gly Arg Leu Thr Lys Pro Ile Val Cys Trp Cys Ile Gly Thr Cys
            740                 745                 750

Ala Thr Met Phe Ser Ser Glu Val Gln Phe Gly His Ala Gly Ala Cys
        755                 760                 765

Ala Asn Gln Ala Ser Glu Thr Ala Val Ala Lys Asn Gln Ala Leu Lys
    770                 775                 780
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```
Glu Ala Gly Val Phe Val Pro Arg Ser Phe Asp Glu Leu Gly Glu Ile
785                 790                 795                 800

Ile Gln Ser Val Tyr Glu Asp Leu Val Ala Asn Gly Val Ile Val Pro
                805                 810                 815

Ala Gln Glu Val Pro Pro Pro Thr Val Pro Met Asp Tyr Ser Trp Ala
            820                 825                 830

Arg Glu Leu Gly Leu Ile Arg Lys Pro Ala Ser Phe Met Thr Ser Ile
        835                 840                 845

Cys Asp Glu Arg Gly Gln Glu Leu Ile Tyr Ala Gly Met Pro Ile Thr
    850                 855                 860

Glu Val Phe Lys Glu Glu Met Gly Ile Gly Gly Ala Leu Gly Leu Leu
865                 870                 875                 880

Trp Phe Gln Lys Arg Leu Pro Lys Tyr Ser Cys Gln Phe Ile Glu Met
                885                 890                 895

Cys Leu Met Val Thr Ala Asp His Gly Pro Ala Val Ser Gly Ala His
            900                 905                 910

Asn Thr Ile Ile Cys Ala Arg Thr Ala Val Glu Leu Val Ser Ser Leu
        915                 920                 925

Thr Ser Gly Leu Leu Thr Ile Gly Asp Arg Phe Gly Gly Ala Leu Asp
    930                 935                 940

Ala Ala Ala Lys Met Phe Ser Lys Ala Phe Asp Ser Gly Ile Ile Pro
945                 950                 955                 960

Met Glu Phe Val Asn Lys Met Lys Lys Glu Gly Lys Leu Ile Met Gly
                965                 970                 975

Ile Gly His Arg Val Lys Ser Ile Asn Asn Pro Asp Met Arg Val Gln
            980                 985                 990

Ile Leu Lys Asp Tyr Val Arg Gln His Phe Pro Ala Thr Pro Leu Leu
        995                1000                1005

Asp Tyr Ala Leu Glu Val Glu Lys Ile Thr Thr Ser Lys Lys Pro Asn
   1010                1015                1020

Leu Ile Leu Asn Val Asp Gly Leu Ile Gly Val Ala Phe Val Asp Met
1025                1030                1035                1040

Leu Arg Asn Cys Gly Ser Phe Thr Arg Glu Glu Ala Asp Glu Tyr Ile
               1045                1050                1055

Asp Ile Gly Ala Leu Asn Gly Ile Phe Val Leu Gly Arg Ser Met Gly
           1060                1065                1070

Phe Ile Gly His Tyr Leu Asp Gln Lys Arg Leu Lys Gln Gly Leu Tyr
       1075                1080                1085

Arg His Pro Trp Asp Asp Ile Ser Tyr Val Leu Pro Glu His Met Ser
   1090                1095                1100

Met
1105


<210> SEQ ID NO 20
<211> LENGTH: 1912
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Ala Ser Gly Leu Gly Ser Pro Ser Pro Cys Ser Ala Gly Ser Glu
  1               5                  10                  15

Glu Glu Asp Met Asp Ala Leu Leu Asn Asn Ser Leu Pro Pro Pro His
             20                  25                  30
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```
Pro Glu Asn Glu Glu Asp Pro Glu Glu Asp Leu Ser Glu Thr Glu Thr
         35                  40                  45

Pro Lys Leu Lys Lys Lys Lys Lys Pro Lys Lys Pro Arg Asp Pro Lys
     50                  55                  60

Ile Pro Lys Ser Lys Arg Gln Lys Lys Glu Arg Met Leu Leu Cys Arg
 65                  70                  75                  80

Gln Leu Gly Asp Ser Ser Gly Glu Gly Pro Glu Phe Val Glu Glu Glu
                 85                  90                  95

Glu Glu Val Ala Leu Arg Ser Asp Ser Glu Gly Ser Asp Tyr Thr Pro
            100                 105                 110

Gly Lys Lys Lys Lys Lys Lys Leu Gly Pro Lys Lys Glu Lys Lys Ser
        115                 120                 125

Lys Ser Lys Arg Lys Glu Glu Glu Glu Glu Asp Asp Asp Asp Asp Asp
    130                 135                 140

Ser Lys Glu Pro Lys Ser Ser Ala Gln Leu Leu Glu Asp Trp Gly Met
145                 150                 155                 160

Glu Asp Ile Asp His Val Phe Ser Glu Glu Asp Tyr Arg Thr Leu Thr
                165                 170                 175

Asn Tyr Lys Ala Phe Ser Gln Phe Val Arg Pro Leu Ile Ala Ala Lys
            180                 185                 190

Asn Pro Lys Ile Ala Val Ser Lys Met Met Met Val Leu Gly Ala Lys
        195                 200                 205

Trp Arg Glu Phe Ser Thr Asn Asn Pro Phe Lys Gly Ser Ser Gly Ala
    210                 215                 220

Ser Val Ala Ala Ala Ala Ala Ala Ala Val Ala Val Val Glu Ser Met
225                 230                 235                 240

Val Thr Ala Thr Glu Val Ala Pro Pro Pro Pro Pro Val Glu Val Pro
                245                 250                 255

Ile Arg Lys Ala Lys Thr Lys Glu Gly Lys Gly Pro Asn Ala Arg Arg
            260                 265                 270

Lys Pro Lys Gly Ser Pro Arg Val Pro Asp Ala Lys Lys Pro Lys Pro
        275                 280                 285

Lys Lys Val Ala Pro Leu Lys Ile Lys Leu Gly Gly Phe Gly Ser Lys
    290                 295                 300

Arg Lys Arg Ser Ser Ser Glu Asp Asp Asp Leu Asp Val Glu Ser Asp
305                 310                 315                 320

Phe Asp Asp Ala Ser Ile Asn Ser Tyr Ser Val Ser Asp Gly Ser Thr
                325                 330                 335

Ser Arg Ser Ser Arg Ser Arg Lys Lys Leu Arg Thr Thr Lys Lys Lys
            340                 345                 350

Lys Lys Gly Glu Glu Glu Val Thr Ala Val Asp Gly Tyr Glu Thr Asp
        355                 360                 365

His Gln Asp Tyr Cys Glu Val Cys Gln Gln Gly Gly Glu Ile Ile Leu
    370                 375                 380

Cys Asp Thr Cys Pro Arg Ala Tyr His Met Val Cys Leu Asp Pro Asp
385                 390                 395                 400

Met Glu Lys Ala Pro Glu Gly Lys Trp Ser Cys Pro His Cys Glu Lys
                405                 410                 415

Glu Gly Ile Gln Trp Glu Ala Lys Glu Asp Asn Ser Glu Gly Glu Glu
            420                 425                 430
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Ile Leu Glu Glu Val Gly Gly Asp Leu Glu Glu Glu Asp Asp His His
        435                 440                 445

Met Glu Phe Cys Arg Val Cys Lys Asp Gly Gly Glu Leu Leu Cys Cys
    450                 455                 460

Asp Thr Cys Pro Ser Ser Tyr His Ile His Cys Leu Asn Pro Pro Leu
465                 470                 475                 480

Pro Glu Ile Pro Asn Gly Glu Trp Leu Cys Pro Arg Cys Thr Cys Pro
                485                 490                 495

Ala Leu Lys Gly Lys Val Gln Lys Ile Leu Ile Trp Lys Trp Gly Gln
            500                 505                 510

Pro Pro Ser Pro Thr Pro Val Pro Arg Pro Pro Asp Ala Asp Pro Asn
        515                 520                 525

Thr Pro Ser Pro Lys Pro Leu Glu Gly Arg Pro Glu Arg Gln Phe Phe
    530                 535                 540

Val Lys Trp Gln Gly Met Ser Tyr Trp His Cys Ser Trp Val Ser Glu
545                 550                 555                 560

Leu Gln Leu Glu Leu His Cys Gln Val Met Phe Arg Asn Tyr Gln Arg
                565                 570                 575

Lys Asn Asp Met Asp Glu Pro Pro Ser Gly Asp Phe Gly Gly Asp Glu
            580                 585                 590

Glu Lys Ser Arg Lys Arg Lys Asn Lys Asp Pro Lys Phe Ala Glu Met
        595                 600                 605

Glu Glu Arg Phe Tyr Arg Tyr Gly Ile Lys Pro Glu Trp Met Met Ile
    610                 615                 620

His Arg Ile Leu Asn His Ser Val Asp Lys Lys Gly His Val His Tyr
625                 630                 635                 640

Leu Ile Lys Trp Arg Asp Leu Pro Tyr Asp Gln Ala Ser Trp Glu Ser
                645                 650                 655

Glu Asp Val Glu Ile Gln Asp Tyr Asp Leu Phe Lys Gln Ser Tyr Trp
            660                 665                 670

Asn His Arg Glu Leu Met Arg Gly Glu Glu Gly Arg Pro Gly Lys Lys
        675                 680                 685

Leu Lys Lys Val Lys Leu Arg Lys Leu Glu Arg Pro Pro Glu Thr Pro
    690                 695                 700

Thr Val Asp Pro Thr Val Lys Tyr Glu Arg Gln Pro Glu Tyr Leu Asp
705                 710                 715                 720

Ala Thr Gly Gly Thr Leu His Pro Tyr Gln Met Glu Gly Leu Asn Trp
                725                 730                 735

Leu Arg Phe Ser Trp Ala Gln Gly Thr Asp Thr Ile Leu Ala Asp Glu
            740                 745                 750

Met Gly Leu Gly Lys Thr Val Gln Thr Ala Val Phe Leu Tyr Ser Leu
        755                 760                 765

Tyr Lys Glu Gly His Ser Lys Gly Pro Phe Leu Val Ser Ala Pro Leu
    770                 775                 780

Ser Thr Ile Ile Asn Trp Glu Arg Glu Phe Glu Met Trp Ala Pro Asp
785                 790                 795                 800

Met Tyr Val Val Thr Tyr Val Gly Asp Lys Asp Ser Arg Ala Ile Ile
                805                 810                 815

Arg Glu Asn Glu Phe Ser Phe Glu Asp Asn Ala Ile Arg Gly Gly Lys
            820                 825                 830

Lys Ala Ser Arg Met Lys Lys Glu Ala Ser Val Lys Phe His Val Leu
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        835                 840                 845

Leu Thr Ser Tyr Glu Leu Ile Thr Ile Asp Met Ala Ile Leu Gly Ser
    850                 855                 860

Ile Asp Trp Ala Cys Leu Ile Val Asp Glu Ala His Arg Leu Lys Asn
865                 870                 875                 880

Asn Gln Ser Lys Phe Phe Arg Val Leu Asn Gly Tyr Ser Leu Gln His
                885                 890                 895

Lys Leu Leu Leu Thr Gly Thr Pro Leu Gln Asn Asn Leu Glu Glu Leu
            900                 905                 910

Phe His Leu Leu Asn Phe Leu Thr Pro Glu Arg Phe His Asn Leu Glu
        915                 920                 925

Gly Phe Leu Glu Glu Phe Ala Asp Ile Ala Lys Glu Asp Gln Ile Lys
    930                 935                 940

Lys Leu His Asp Met Leu Gly Pro His Met Leu Arg Arg Leu Lys Ala
945                 950                 955                 960

Asp Val Phe Lys Asn Met Pro Ser Lys Thr Glu Leu Ile Val Arg Val
                965                 970                 975

Glu Leu Ser Pro Met Gln Lys Lys Tyr Tyr Lys Tyr Ile Leu Thr Arg
            980                 985                 990

Asn Phe Glu Ala Leu Asn Ala Arg Gly Gly Gly Asn Gln Val Ser Leu
        995                1000                1005

Leu Asn Val Val Met Asp Leu Lys Lys Cys Cys Asn His Pro Tyr Leu
   1010                1015                1020

Phe Pro Val Ala Ala Met Glu Ala Pro Lys Met Pro Asn Gly Met Tyr
1025                1030                1035                1040

Asp Gly Ser Ala Leu Ile Arg Ala Ser Gly Lys Leu Leu Leu Leu Gln
               1045                1050                1055

Lys Met Leu Lys Asn Leu Lys Glu Gly Gly His Arg Val Leu Ile Phe
           1060                1065                1070

Ser Gln Met Thr Lys Met Leu Asp Leu Leu Glu Asp Phe Leu Glu His
       1075                1080                1085

Glu Gly Tyr Lys Tyr Glu Arg Ile Asp Gly Gly Ile Thr Gly Asn Met
   1090                1095                1100

Arg Gln Glu Ala Ile Asp Arg Phe Asn Ala Pro Gly Ala Gln Gln Phe
1105                1110                1115                1120

Cys Phe Leu Leu Ser Thr Arg Ala Gly Gly Leu Gly Ile Asn Leu Ala
               1125                1130                1135

Thr Ala Asp Thr Val Ile Ile Tyr Asp Ser Asp Trp Asn Pro His Asn
           1140                1145                1150

Asp Ile Gln Ala Phe Ser Arg Ala His Arg Ile Gly Gln Asn Lys Lys
       1155                1160                1165

Val Met Ile Tyr Arg Phe Val Thr Arg Ala Ser Val Glu Glu Arg Ile
   1170                1175                1180

Thr Gln Val Ala Lys Lys Lys Met Met Leu Thr His Leu Val Val Arg
1185                1190                1195                1200

Pro Gly Leu Gly Ser Lys Thr Gly Ser Met Ser Lys Gln Glu Leu Asp
               1205                1210                1215

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

Asp Gly Gly Gly Asp Asn Lys Glu Gly Glu Asp Ser Ser Val Ile His
       1235                1240                1245
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Tyr Asp Asp Lys Ala Ile Glu Arg Leu Leu Asp Arg Asn Gln Asp Glu
   1250                1255                1260

Thr Glu Asp Thr Glu Leu Gln Gly Met Asn Glu Tyr Leu Ser Ser Phe
1265                1270                1275                1280

Lys Val Ala Gln Tyr Val Val Arg Glu Glu Glu Met Gly Glu Glu Glu
               1285                1290                1295

Glu Val Glu Arg Glu Ile Ile Lys Gln Glu Glu Ser Val Asp Pro Asp
           1300                1305                1310

Tyr Trp Glu Lys Leu Leu Arg His His Tyr Glu Gln Gln Gln Glu Asp
       1315                1320                1325

Leu Ala Arg Asn Leu Gly Lys Gly Lys Arg Ile Arg Lys Gln Val Asn
   1330                1335                1340

Tyr Asn Asp Gly Ser Gln Glu Asp Arg Asp Trp Gln Asp Asp Gln Ser
1345                1350                1355                1360

Asp Asn Gln Ser Asp Tyr Ser Val Ala Ser Glu Glu Gly Asp Glu Asp
               1365                1370                1375

Phe Asp Glu Arg Ser Glu Ala Pro Arg Arg Pro Ser Arg Lys Gly Leu
           1380                1385                1390

Arg Asn Asp Lys Asp Lys Pro Leu Pro Pro Leu Leu Ala Arg Val Gly
       1395                1400                1405

Gly Asn Ile Glu Val Leu Gly Phe Asn Ala Arg Gln Arg Lys Ala Phe
   1410                1415                1420

Leu Asn Ala Ile Met Arg Tyr Gly Met Pro Pro Gln Asp Ala Phe Thr
1425                1430                1435                1440

Thr Gln Trp Leu Val Arg Asp Leu Arg Gly Lys Ser Glu Lys Glu Phe
               1445                1450                1455

Lys Ala Tyr Val Ser Leu Phe Met Arg His Leu Cys Glu Pro Gly Ala
           1460                1465                1470

Asp Gly Ala Glu Thr Phe Ala Asp Gly Val Pro Arg Glu Gly Leu Ser
       1475                1480                1485

Arg Gln His Val Leu Thr Arg Ile Gly Val Met Ser Leu Ile Arg Lys
   1490                1495                1500

Lys Val Gln Glu Phe Glu His Val Asn Gly Arg Trp Ser Met Pro Glu
1505                1510                1515                1520

Leu Ala Glu Val Glu Glu Asn Lys Lys Met Ser Gln Pro Gly Ser Pro
               1525                1530                1535

Ser Pro Lys Thr Pro Thr Pro Ser Thr Pro Gly Asp Thr Gln Pro Asn
           1540                1545                1550

Thr Pro Ala Pro Val Pro Pro Ala Glu Asp Gly Ile Lys Ile Glu Glu
       1555                1560                1565

Asn Ser Leu Lys Glu Glu Glu Ser Ile Glu Gly Glu Lys Glu Val Lys
   1570                1575                1580

Ser Thr Ala Pro Glu Thr Ala Ile Glu Cys Thr Gln Ala Pro Ala Pro
1585                1590                1595                1600

Ala Ser Glu Asp Glu Lys Val Val Val Glu Pro Pro Glu Gly Glu Glu
               1605                1610                1615

Lys Val Glu Lys Ala Glu Val Lys Glu Arg Thr Glu Glu Pro Met Glu
           1620                1625                1630

Thr Glu Pro Lys Gly Ala Ala Asp Val Glu Lys Val Glu Glu Lys Ser
       1635                1640                1645
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Ala Ile Asp Leu Thr Pro Ile Val Val Glu Asp Lys Glu Glu Lys Lys
   1650                1655                1660

Glu Glu Glu Glu Lys Lys Glu Val Met Leu Gln Asn Gly Glu Thr Pro
1665                1670                1675                1680

Lys Asp Leu Asn Asp Glu Lys Gln Lys Lys Asn Ile Lys Gln Arg Phe
                1685                1690                1695

Met Phe Asn Ile Ala Asp Gly Gly Phe Thr Glu Leu His Ser Leu Trp
            1700                1705                1710

Gln Asn Glu Glu Arg Ala Ala Thr Val Thr Lys Lys Thr Tyr Glu Ile
        1715                1720                1725

Trp His Arg Arg His Asp Tyr Trp Leu Leu Ala Gly Ile Ile Asn His
    1730                1735                1740

Gly Tyr Ala Arg Trp Gln Asp Ile Gln Asn Asp Pro Arg Tyr Ala Ile
1745                1750                1755                1760

Leu Asn Glu Pro Phe Lys Gly Glu Met Asn Arg Gly Asn Phe Leu Glu
                1765                1770                1775

Ile Lys Asn Lys Phe Leu Ala Arg Arg Phe Lys Leu Leu Glu Gln Ala
            1780                1785                1790

Leu Val Ile Glu Glu Gln Leu Arg Arg Ala Ala Tyr Leu Asn Met Ser
        1795                1800                1805

Glu Asp Pro Ser His Pro Ser Met Ala Leu Asn Thr Arg Phe Ala Glu
    1810                1815                1820

Val Glu Cys Leu Ala Glu Ser His Gln His Leu Ser Lys Glu Ser Met
1825                1830                1835                1840

Ala Gly Asn Lys Pro Ala Asn Ala Val Leu His Lys Val Leu Lys Gln
                1845                1850                1855

Leu Glu Glu Leu Leu Ser Asp Met Lys Ala Asp Val Thr Arg Leu Pro
            1860                1865                1870

Ala Thr Ile Ala Arg Ile Pro Pro Val Ala Val Arg Leu Gln Met Ser
        1875                1880                1885

Glu Arg Asn Ile Leu Ser Arg Leu Ala Asn Arg Ala Pro Glu Pro Thr
    1890                1895                1900

Pro Gln Gln Val Ala Gln Gln Gln
1905                1910


<210> SEQ ID NO 21
<211> LENGTH: 1857
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Glu Gln Leu Thr Thr Leu Pro Arg Pro Gly Asp Pro Gly Ala Met
  1               5                  10                  15

Glu Pro Trp Ala Leu Pro Thr Trp His Ser Trp Thr Pro Gly Arg Gly
             20                  25                  30

Gly Glu Pro Ser Ser Ala Ala Pro Ser Ile Ala Asp Thr Pro Pro Ala
         35                  40                  45

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

Gly Asp Gly Ser Ser Arg Pro Val Gly Gly Thr Asp Pro Glu Gly Ala
 65                  70                  75                  80

Glu Ala Cys Leu Pro Ser Leu Gly Gln Gln Ala Ser Ser Ser Gly Pro
                 85                  90                  95
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Ala Cys Gln Arg Pro Glu Asp Glu Glu Val Glu Ala Phe Leu Lys Ala
            100                 105                 110

Lys Leu Asn Met Ser Phe Gly Asp Arg Pro Asn Leu Glu Leu Leu Arg
        115                 120                 125

Ala Leu Gly Glu Leu Arg Gln Arg Cys Ala Ile Leu Lys Glu Glu Asn
    130                 135                 140

Gln Met Leu Arg Lys Ser Ser Phe Pro Glu Thr Glu Glu Lys Val Arg
145                 150                 155                 160

Arg Leu Lys Arg Lys Asn Ala Glu Leu Ala Val Ile Ala Lys Arg Leu
                165                 170                 175

Glu Glu Arg Ala Arg Lys Leu Gln Glu Thr Asn Leu Arg Val Val Ser
            180                 185                 190

Ala Pro Leu Pro Arg Pro Gly Thr Ser Leu Glu Leu Cys Arg Lys Ala
        195                 200                 205

Leu Ala Arg Gln Arg Ala Arg Asp Leu Ser Glu Thr Ala Ser Ala Leu
    210                 215                 220

Leu Ala Lys Asp Lys Gln Ile Ala Ala Leu Gln Arg Glu Cys Arg Glu
225                 230                 235                 240

Leu Gln Ala Arg Leu Thr Leu Val Gly Lys Glu Gly Pro Gln Trp Leu
                245                 250                 255

His Val Arg Asp Phe Asp Arg Leu Leu Arg Glu Ser Gln Arg Glu Val
            260                 265                 270

Leu Arg Leu Gln Arg Gln Ile Ala Leu Arg Asn Gln Arg Glu Thr Leu
        275                 280                 285

Pro Leu Pro Pro Ser Trp Pro Pro Gly Pro Ala Leu Gln Ala Arg Ala
    290                 295                 300

Gly Ala Pro Ala Pro Gly Ala Pro Gly Glu Ala Thr Pro Gln Glu Asp
305                 310                 315                 320

Ala Asp Asn Leu Pro Val Ile Leu Gly Glu Pro Glu Lys Glu Gln Arg
                325                 330                 335

Val Gln Gln Leu Glu Ser Glu Leu Ser Lys Lys Arg Lys Lys Cys Glu
            340                 345                 350

Ser Leu Glu Gln Glu Ala Arg Lys Lys Gln Arg Arg Cys Glu Glu Leu
        355                 360                 365

Glu Leu Gln Leu Arg Gln Ala Gln Asn Glu Asn Ala Arg Leu Val Glu
    370                 375                 380

Glu Asn Ser Arg Leu Ser Gly Arg Ala Thr Glu Lys Glu Gln Val Glu
385                 390                 395                 400

Trp Glu Asn Ala Glu Leu Arg Gly Gln Leu Leu Gly Val Thr Gln Glu
                405                 410                 415

Arg Asp Ser Ala Leu Arg Lys Ser Gln Gly Leu Gln Ser Lys Leu Glu
            420                 425                 430

Ser Leu Glu Gln Val Leu Lys His Met Arg Glu Val Ala Gln Arg Arg
        435                 440                 445

Gln Gln Leu Glu Val Glu His Glu Gln Ala Arg Leu Ser Leu Arg Glu
    450                 455                 460

Lys Gln Glu Glu Val Arg Arg Leu Gln Gln Ala Gln Ala Glu Ala Gln
465                 470                 475                 480

Arg Glu His Glu Gly Ala Val Gln Leu Leu Glu Ser Thr Leu Asp Ser
                485                 490                 495
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Met Gln Ala Arg Val Arg Glu Leu Glu Glu Gln Cys Arg Ser Gln Thr
            500                 505                 510

Glu Gln Phe Ser Leu Leu Ala Gln Glu Leu Gln Ala Phe Arg Leu His
        515                 520                 525

Pro Gly Pro Leu Asp Leu Leu Thr Ser Ala Leu Asp Cys Gly Ser Leu
    530                 535                 540

Gly Asp Cys Pro Pro Pro Pro Cys Cys Cys Ser Ile Pro Gln Pro Cys
545                 550                 555                 560

Arg Gly Ser Gly Pro Lys Asp Leu Asp Leu Pro Pro Gly Ser Pro Gly
                565                 570                 575

Arg Cys Thr Pro Lys Ser Ser Glu Pro Ala Pro Ala Thr Leu Thr Gly
            580                 585                 590

Val Pro Arg Arg Thr Ala Lys Lys Ala Glu Ser Leu Ser Asn Ser Ser
        595                 600                 605

His Ser Glu Ser Ile His Asn Ser Pro Lys Ser Cys Pro Thr Pro Glu
    610                 615                 620

Val Asp Thr Ala Ser Glu Val Glu Glu Leu Glu Ala Asp Ser Val Ser
625                 630                 635                 640

Leu Leu Pro Ala Ala Pro Glu Gly Ser Arg Gly Gly Ala Arg Ile Gln
                645                 650                 655

Val Phe Leu Ala Arg Tyr Ser Tyr Asn Pro Phe Glu Gly Pro Asn Glu
            660                 665                 670

Asn Pro Glu Ala Glu Leu Pro Leu Thr Ala Gly Glu Tyr Ile Tyr Ile
        675                 680                 685

Tyr Gly Asn Met Asp Glu Asp Gly Phe Phe Glu Gly Glu Leu Met Asp
    690                 695                 700

Gly Arg Arg Gly Leu Val Pro Ser Asn Phe Val Glu Arg Val Ser Asp
705                 710                 715                 720

Asp Asp Leu Leu Thr Ser Leu Pro Pro Glu Leu Ala Asp Leu Ser His
                725                 730                 735

Ser Ser Gly Pro Glu Leu Ser Phe Leu Ser Val Gly Gly Gly Gly Ser
            740                 745                 750

Ser Ser Gly Gly Gln Ser Ser Val Gly Arg Ser Gln Pro Arg Pro Glu
        755                 760                 765

Glu Glu Asp Ala Gly Asp Glu Leu Ser Leu Ser Pro Ser Pro Glu Gly
    770                 775                 780

Leu Gly Glu Pro Pro Ala Val Pro Tyr Pro Arg Arg Leu Val Val Leu
785                 790                 795                 800

Lys Gln Leu Ala His Ser Val Val Leu Ala Trp Glu Pro Pro Pro Glu
                805                 810                 815

Gln Val Glu Leu His Gly Phe His Ile Cys Val Asn Gly Glu Leu Arg
            820                 825                 830

Gln Ala Leu Gly Pro Gly Ala Pro Pro Lys Ala Val Leu Glu Asn Leu
        835                 840                 845

Asp Leu Trp Ala Gly Pro Leu His Ile Ser Val Gln Ala Leu Thr Ser
    850                 855                 860

Arg Gly Ser Ser Asp Pro Leu Arg Cys Cys Leu Ala Val Gly Ala Arg
865                 870                 875                 880

Ala Gly Val Val Pro Ser Gln Leu Arg Val His Arg Leu Thr Ala Thr
                885                 890                 895

Ser Ala Glu Ile Thr Trp Val Pro Gly Asn Ser Asn Leu Ala His Ala
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           900                 905                 910

Ile Tyr Leu Asn Gly Glu Glu Cys Pro Pro Ala Ser Pro Ser Thr Tyr
        915                 920                 925

Trp Ala Thr Phe Cys His Leu Arg Pro Gly Thr Pro Tyr Gln Ala Gln
    930                 935                 940

Val Glu Ala Gln Leu Pro Pro Gln Gly Pro Trp Glu Pro Gly Trp Glu
945                 950                 955                 960

Arg Leu Glu Gln Arg Ala Ala Thr Leu Gln Phe Thr Thr Leu Pro Ala
                965                 970                 975

Gly Pro Pro Asp Ala Pro Leu Asp Val Gln Ile Glu Pro Gly Pro Ser
            980                 985                 990

Pro Gly Ile Leu Ile Ile Ser Trp Leu Pro Val Thr Ile Asp Ala Ala
        995                1000                1005

Gly Thr Ser Asn Gly Val Arg Val Thr Gly Tyr Ala Ile Tyr Ala Asp
   1010                1015                1020

Gly Gln Lys Ile Met Glu Val Ala Ser Pro Thr Ala Gly Ser Val Leu
1025                1030                1035                1040

Val Glu Leu Ser Gln Leu Gln Leu Leu Gln Val Cys Arg Glu Val Val
                1045                1050                1055

Val Arg Thr Met Ser Pro His Gly Glu Ser Ala Asp Ser Ile Pro Ala
            1060                1065                1070

Pro Ile Thr Pro Ala Leu Ala Pro Ala Ser Leu Pro Ala Arg Val Ser
        1075                1080                1085

Cys Pro Ser Pro His Pro Ser Pro Glu Ala Arg Ala Pro Leu Ala Ser
   1090                1095                1100

Ala Ser Pro Gly Pro Gly Asp Pro Ser Ser Pro Leu Gln His Pro Ala
1105                1110                1115                1120

Pro Leu Gly Thr Gln Glu Pro Pro Gly Ala Pro Pro Ala Ser Pro Ser
                1125                1130                1135

Arg Glu Met Ala Lys Gly Ser His Glu Asp Pro Pro Ala Pro Cys Ser
            1140                1145                1150

Gln Glu Glu Ala Gly Ala Ala Val Leu Gly Thr Ser Glu Glu Arg Thr
        1155                1160                1165

Ala Ser Thr Ser Thr Leu Gly Glu Lys Asp Pro Gly Pro Ala Ala Pro
   1170                1175                1180

Ser Leu Ala Lys Gln Glu Ala Glu Trp Thr Ala Gly Glu Ala Cys Pro
1185                1190                1195                1200

Ala Ser Ser Ser Thr Gln Gly Ala Arg Ala Gln Gln Ala Pro Asn Thr
                1205                1210                1215

Glu Met Cys Gln Gly Gly Asp Pro Gly Ser Gly Leu Arg Pro Arg Ala
            1220                1225                1230

Glu Lys Glu Asp Thr Ala Glu Leu Gly Val His Leu Val Asn Ser Leu
        1235                1240                1245

Val Asp His Gly Arg Asn Ser Asp Leu Ser Asp Ile Gln Glu Glu Glu
   1250                1255                1260

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Leu Gly Ser Arg Thr Cys
1265                1270                1275                1280

Ser Phe Gln Lys Gln Val Ala Gly Asn Ser Ile Arg Glu Asn Gly Ala
                1285                1290                1295

Lys Ser Gln Pro Asp Pro Phe Cys Glu Thr Asp Ser Asp Glu Glu Ile
            1300                1305                1310
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```
Leu Glu Gln Ile Leu Glu Leu Pro Leu Gln Gln Phe Cys Ser Lys Lys
       1315                1320                1325

Leu Phe Ser Ile Pro Glu Glu Glu Glu Glu Glu Glu Glu Asp Glu Glu
   1330                1335                1340

Glu Glu Lys Ser Gly Ala Gly Cys Ser Ser Arg Asp Pro Gly Pro Pro
1345                1350                1355                1360

Glu Pro Ala Leu Leu Gly Leu Gly Cys Asp Ser Gly Gln Pro Arg Arg
               1365                1370                1375

Pro Gly Gln Cys Pro Leu Ser Pro Glu Ser Ser Arg Ala Gly Asp Cys
           1380                1385                1390

Leu Glu Asp Met Pro Gly Leu Val Gly Gly Ser Ser Arg Arg Arg Gly
       1395                1400                1405

Gly Gly Ser Pro Glu Lys Pro Pro Ser Arg Arg Arg Pro Pro Asp Pro
   1410                1415                1420

Arg Glu His Cys Ser Arg Leu Leu Ser Asn Asn Gly Pro Gln Ala Ser
1425                1430                1435                1440

Gly Arg Leu Gly Pro Thr Arg Glu Arg Gly Gly Leu Pro Val Ile Glu
               1445                1450                1455

Gly Pro Arg Thr Gly Leu Glu Ala Ser Gly Arg Gly Arg Leu Gly Pro
           1460                1465                1470

Ser Arg Arg Cys Ser Arg Gly Arg Ala Leu Glu Pro Gly Leu Ala Ser
       1475                1480                1485

Cys Leu Ser Pro Lys Cys Leu Glu Ile Ser Ile Glu Tyr Asp Ser Glu
   1490                1495                1500

Asp Glu Gln Glu Ala Gly Ser Gly Gly Ile Ser Ile Thr Ser Ser Cys
1505                1510                1515                1520

Tyr Pro Gly Asp Arg Glu Ala Trp Gly Thr Ala Thr Val Gly Arg Pro
               1525                1530                1535

Arg Gly Pro Pro Lys Ala Asn Ser Gly Pro Lys Pro Tyr Pro Arg Leu
           1540                1545                1550

Pro Ala Trp Glu Lys Gly Glu Pro Glu Arg Arg Gly Arg Ser Ala Thr
       1555                1560                1565

Gly Arg Ala Lys Glu Pro Leu Ser Arg Ala Thr Glu Thr Gly Glu Ala
   1570                1575                1580

Arg Gly Gln Asp Gly Ser Gly Arg Arg Gly Pro Gln Lys Arg Gly Val
1585                1590                1595                1600

Arg Val Leu Arg Pro Ser Thr Ala Glu Leu Val Pro Ala Arg Ser Pro
               1605                1610                1615

Ser Glu Thr Leu Ala Tyr Gln His Leu Pro Val Arg Ile Phe Val Ala
           1620                1625                1630

Leu Phe Asp Tyr Asp Pro Val Ser Met Ser Pro Asn Pro Asp Ala Gly
       1635                1640                1645

Glu Glu Glu Leu Pro Phe Arg Glu Gly Gln Ile Leu Lys Val Phe Gly
   1650                1655                1660

Asp Lys Asp Ala Asp Gly Phe Tyr Gln Gly Glu Gly Gly Gly Arg Thr
1665                1670                1675                1680

Gly Tyr Ile Pro Cys Asn Met Val Ala Glu Val Ala Val Asp Ser Pro
               1685                1690                1695

Ala Gly Arg Gln Gln Leu Leu Gln Arg Gly Tyr Leu Ser Pro Asp Ile
           1700                1705                1710
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Leu Leu Glu Gly Ser Gly Asn Gly Pro Phe Val Tyr Ser Thr Ala His
       1715                1720                1725

Thr Thr Gly Pro Pro Pro Lys Pro Arg Arg Ser Lys Lys Ala Glu Ser
   1730                1735                1740

Glu Gly Pro Ala Gln Pro Cys Pro Gly Pro Pro Lys Leu Val Pro Ser
1745                1750                1755                1760

Ala Asp Leu Lys Ala Pro His Ser Met Val Ala Ala Phe Asp Tyr Asn
               1765                1770                1775

Pro Gln Glu Ser Ser Pro Asn Met Asp Val Glu Ala Glu Leu Pro Phe
           1780                1785                1790

Arg Ala Gly Asp Val Ile Thr Val Phe Gly Gly Met Asp Asp Asp Gly
       1795                1800                1805

Phe Tyr Tyr Gly Glu Leu Asn Gly Gln Arg Gly Leu Val Pro Ser Asn
   1810                1815                1820

Phe Leu Glu Gly Pro Gly Pro Glu Ala Gly Gly Leu Asp Arg Glu Pro
1825                1830                1835                1840

Arg Thr Pro Gln Ala Glu Ser Gln Arg Thr Arg Arg Arg Arg Val Gln
               1845                1850                1855

Cys


<210> SEQ ID NO 22
<211> LENGTH: 806
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Ser Ser Ser Pro Val Asn Val Lys Lys Leu Lys Val Ser Glu Leu
  1               5                  10                  15

Lys Glu Glu Leu Lys Lys Arg Arg Leu Ser Asp Lys Gly Leu Lys Ala
             20                  25                  30

Glu Leu Met Glu Arg Leu Gln Ala Ala Leu Asp Asp Glu Glu Ala Gly
         35                  40                  45

Gly Arg Pro Ala Met Glu Pro Gly Asn Gly Ser Leu Asp Leu Gly Gly
     50                  55                  60

Asp Ser Ala Gly Arg Ser Gly Ala Gly Leu Glu Gln Glu Ala Ala Ala
 65                  70                  75                  80

Gly Gly Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Gly Ile
                 85                  90                  95

Ser Ala Leu Asp Gly Asp Gln Met Glu Leu Gly Glu Glu Asn Gly Ala
            100                 105                 110

Ala Gly Ala Ala Asp Ser Gly Pro Met Glu Glu Glu Glu Ala Ala Ser
        115                 120                 125

Glu Asp Glu Asn Gly Asp Asp Gln Gly Phe Gln Glu Gly Glu Asp Glu
    130                 135                 140

Leu Gly Asp Glu Glu Glu Gly Ala Gly Asp Glu Asn Gly His Gly Glu
145                 150                 155                 160

Gln Gln Pro Gln Pro Pro Ala Thr Gln Gln Gln Gln Pro Gln Gln Gln
                165                 170                 175

Arg Gly Ala Ala Lys Glu Ala Ala Gly Lys Ser Ser Gly Pro Thr Ser
            180                 185                 190

Leu Phe Ala Val Thr Val Ala Pro Pro Gly Ala Arg Gln Gly Gln Gln
        195                 200                 205
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```
Gln Ala Gly Gly Asp Gly Lys Thr Glu Gln Lys Gly Gly Asp Lys Lys
    210                 215                 220

Arg Gly Val Lys Arg Pro Arg Glu Asp His Gly Arg Gly Tyr Phe Glu
225                 230                 235                 240

Tyr Ile Glu Glu Asn Lys Tyr Ser Arg Ala Lys Ser Pro Gln Pro Pro
                245                 250                 255

Val Glu Glu Glu Asp Glu His Phe Asp Asp Thr Val Val Cys Leu Asp
            260                 265                 270

Thr Tyr Asn Cys Asp Leu His Phe Lys Ile Ser Arg Asp Arg Leu Ser
        275                 280                 285

Ala Ser Ser Leu Thr Met Glu Ser Phe Ala Phe Leu Trp Ala Gly Gly
    290                 295                 300

Arg Ala Ser Tyr Gly Val Ser Lys Gly Lys Val Cys Phe Glu Met Lys
305                 310                 315                 320

Val Thr Glu Lys Ile Pro Val Arg His Leu Tyr Thr Lys Asp Ile Asp
                325                 330                 335

Ile His Glu Val Arg Ile Gly Trp Ser Leu Thr Thr Ser Gly Met Leu
            340                 345                 350

Leu Gly Glu Glu Glu Phe Ser Tyr Gly Tyr Ser Leu Lys Gly Ile Lys
        355                 360                 365

Thr Cys Asn Cys Glu Thr Glu Asp Tyr Gly Glu Lys Phe Asp Glu Asn
    370                 375                 380

Asp Val Ile Thr Cys Phe Ala Asn Phe Glu Ser Asp Glu Val Glu Leu
385                 390                 395                 400

Ser Tyr Ala Lys Asn Gly Gln Asp Leu Gly Val Ala Phe Lys Ile Ser
                405                 410                 415

Lys Glu Val Leu Ala Gly Arg Pro Leu Phe Pro His Val Leu Cys His
            420                 425                 430

Asn Cys Ala Val Glu Phe Asn Phe Gly Gln Lys Glu Lys Pro Tyr Phe
        435                 440                 445

Pro Ile Pro Glu Glu Tyr Thr Phe Ile Gln Asn Val Pro Leu Glu Asp
    450                 455                 460

Arg Val Arg Gly Pro Lys Gly Pro Glu Glu Lys Lys Asp Cys Glu Val
465                 470                 475                 480

Val Met Met Ile Gly Leu Pro Gly Ala Gly Lys Thr Thr Trp Val Thr
                485                 490                 495

Lys His Ala Ala Glu Asn Pro Gly Lys Tyr Asn Ile Leu Gly Thr Asn
            500                 505                 510

Thr Ile Met Asp Lys Met Met Val Ala Gly Phe Lys Lys Gln Met Ala
        515                 520                 525

Asp Thr Gly Lys Leu Asn Thr Leu Leu Gln Arg Ala Pro Gln Cys Leu
    530                 535                 540

Gly Lys Phe Ile Glu Ile Ala Ala Arg Lys Lys Arg Asn Phe Ile Leu
545                 550                 555                 560

Asp Gln Thr Asn Val Ser Ala Ala Ala Gln Arg Arg Lys Met Cys Leu
                565                 570                 575

Phe Ala Gly Phe Gln Arg Lys Ala Val Val Val Cys Pro Lys Asp Glu
            580                 585                 590

Asp Tyr Lys Gln Arg Thr Gln Lys Lys Ala Glu Val Glu Gly Lys Asp
        595                 600                 605

Leu Pro Glu His Ala Val Leu Lys Met Lys Gly Asn Phe Thr Leu Pro
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    610                 615                 620

Glu Val Ala Glu Cys Phe Asp Glu Ile Thr Tyr Val Glu Leu Gln Lys
625                 630                 635                 640

Glu Glu Ala Gln Lys Leu Leu Glu Gln Tyr Lys Glu Glu Ser Lys Lys
                645                 650                 655

Ala Leu Pro Pro Glu Lys Lys Gln Asn Thr Gly Ser Lys Lys Ser Asn
            660                 665                 670

Lys Asn Lys Ser Gly Lys Asn Gln Phe Asn Arg Gly Gly Gly His Arg
        675                 680                 685

Gly Arg Gly Gly Phe Asn Met Arg Gly Gly Asn Phe Arg Gly Gly Ala
    690                 695                 700

Pro Gly Asn Arg Gly Gly Tyr Asn Arg Arg Gly Asn Met Pro Gln Arg
705                 710                 715                 720

Gly Gly Gly Gly Gly Gly Ser Gly Gly Ile Gly Tyr Pro Tyr Pro Arg
                725                 730                 735

Ala Pro Val Phe Pro Gly Arg Gly Ser Tyr Ser Asn Arg Gly Asn Tyr
            740                 745                 750

Asn Arg Gly Gly Met Pro Asn Arg Gly Asn Tyr Asn Gln Asn Phe Arg
        755                 760                 765

Gly Arg Gly Asn Asn Arg Gly Tyr Lys Asn Gln Ser Gln Gly Tyr Asn
    770                 775                 780

Gln Trp Gln Gln Gly Gln Phe Trp Gly Gln Lys Pro Trp Ser Gln His
785                 790                 795                 800

Tyr His Gln Gly Tyr Tyr
                805


<210> SEQ ID NO 23
<211> LENGTH: 824
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Met Ser Ser Ser Pro Val Asn Val Lys Lys Leu Lys Val Ser Glu Leu
  1               5                  10                  15

Lys Glu Glu Leu Lys Lys Arg Arg Leu Ser Asp Lys Gly Leu Lys Ala
             20                  25                  30

Glu Leu Met Glu Arg Leu Gln Ala Ala Leu Asp Asp Glu Glu Ala Gly
         35                  40                  45

Gly Arg Pro Ala Met Glu Pro Gly Asn Gly Ser Leu Asp Leu Gly Gly
     50                  55                  60

Asp Ser Ala Gly Arg Ser Gly Ala Gly Leu Glu Gln Glu Ala Ala Ala
 65                  70                  75                  80

Gly Gly Asp Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Gly Ile
                 85                  90                  95

Ser Ala Leu Asp Gly Asp Gln Met Glu Leu Gly Glu Glu Asn Gly Ala
            100                 105                 110

Ala Gly Ala Ala Asp Ser Gly Pro Met Glu Glu Glu Glu Ala Ala Ser
        115                 120                 125

Glu Asp Glu Asn Gly Asp Asp Gln Gly Phe Gln Glu Gly Glu Asp Glu
    130                 135                 140

Leu Gly Asp Glu Glu Glu Glu Gly Ala Gly Asp Glu Asn Gly His Gly Glu
145                 150                 155                 160
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Gln Gln Pro Gln Pro Pro Ala Thr Gln Gln Gln Gln Pro Gln Gln Gln
                165                 170                 175

Arg Gly Ala Ala Lys Glu Ala Ala Gly Lys Ser Ser Gly Pro Thr Ser
            180                 185                 190

Leu Phe Ala Val Thr Val Ala Pro Pro Gly Ala Arg Gln Gly Gln Gln
        195                 200                 205

Gln Ala Gly Gly Lys Lys Lys Ala Glu Gly Gly Gly Gly Gly Gly Arg
    210                 215                 220

Pro Gly Ala Pro Ala Gly Asp Gly Lys Thr Glu Gln Lys Gly Gly Asp
225                 230                 235                 240

Lys Lys Arg Gly Val Lys Arg Pro Arg Glu Asp His Gly Arg Gly Tyr
                245                 250                 255

Phe Glu Tyr Ile Glu Glu Asn Lys Tyr Ser Arg Ala Lys Ser Pro Gln
            260                 265                 270

Pro Pro Val Glu Glu Glu Asp Glu His Phe Asp Asp Thr Val Val Cys
        275                 280                 285

Leu Asp Thr Tyr Asn Cys Asp Leu His Phe Lys Ile Ser Arg Asp Arg
    290                 295                 300

Leu Ser Ala Ser Ser Leu Thr Met Glu Ser Phe Ala Phe Leu Trp Ala
305                 310                 315                 320

Gly Gly Arg Ala Ser Tyr Gly Val Ser Lys Gly Lys Val Cys Phe Glu
                325                 330                 335

Met Lys Val Thr Glu Lys Ile Pro Val Arg His Leu Tyr Thr Lys Asp
            340                 345                 350

Ile Asp Ile His Glu Val Arg Ile Gly Trp Ser Leu Thr Thr Ser Gly
        355                 360                 365

Met Leu Leu Gly Glu Glu Glu Phe Ser Tyr Gly Tyr Ser Leu Lys Gly
    370                 375                 380

Ile Lys Thr Cys Asn Cys Glu Thr Glu Asp Tyr Gly Glu Lys Phe Asp
385                 390                 395                 400

Glu Asn Asp Val Ile Thr Cys Phe Ala Asn Phe Glu Ser Asp Glu Val
                405                 410                 415

Glu Leu Ser Tyr Ala Lys Asn Gly Gln Asp Leu Gly Val Ala Phe Lys
            420                 425                 430

Ile Ser Lys Glu Val Leu Ala Gly Arg Pro Leu Phe Pro His Val Leu
        435                 440                 445

Cys His Asn Cys Ala Val Glu Phe Asn Phe Gly Gln Lys Glu Lys Pro
    450                 455                 460

Tyr Phe Pro Ile Pro Glu Glu Tyr Thr Phe Ile Gln Asn Val Pro Leu
465                 470                 475                 480

Glu Asp Arg Val Arg Gly Pro Lys Gly Pro Glu Glu Lys Lys Asp Cys
                485                 490                 495

Glu Val Val Met Met Ile Gly Leu Pro Gly Ala Gly Lys Thr Thr Trp
            500                 505                 510

Val Thr Lys His Ala Ala Glu Asn Pro Gly Lys Tyr Asn Ile Leu Gly
        515                 520                 525

Thr Asn Thr Ile Met Asp Lys Met Met Val Ala Gly Phe Lys Lys Gln
    530                 535                 540

Met Ala Asp Thr Gly Lys Leu Asn Thr Leu Leu Gln Arg Ala Pro Gln
545                 550                 555                 560

Cys Leu Gly Lys Phe Ile Glu Ile Ala Ala Arg Lys Lys Arg Asn Phe
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               565                 570                 575

Ile Leu Asp Gln Thr Asn Val Ser Ala Ala Ala Gln Arg Arg Lys Met
            580                 585                 590

Cys Leu Phe Ala Gly Phe Gln Arg Lys Ala Val Val Val Cys Pro Lys
        595                 600                 605

Asp Glu Asp Tyr Lys Gln Arg Thr Gln Lys Lys Ala Glu Val Glu Gly
    610                 615                 620

Lys Asp Leu Pro Glu His Ala Val Leu Lys Met Lys Gly Asn Phe Thr
625                 630                 635                 640

Leu Pro Glu Val Ala Glu Cys Phe Asp Glu Ile Thr Tyr Val Glu Leu
                645                 650                 655

Gln Lys Glu Glu Ala Gln Lys Leu Leu Glu Gln Tyr Lys Glu Glu Ser
            660                 665                 670

Lys Lys Ala Leu Pro Pro Glu Lys Lys Gln Asn Thr Gly Ser Lys Lys
        675                 680                 685

Ser Asn Lys Asn Lys Ser Gly Lys Asn Gln Phe Asn Arg Gly Gly Gly
    690                 695                 700

His Arg Gly Arg Gly Gly Leu Asn Met Arg Gly Gly Asn Phe Arg Gly
705                 710                 715                 720

Gly Ala Pro Gly Asn Arg Gly Gly Tyr Asn Arg Arg Gly Asn Met Pro
                725                 730                 735

Gln Arg Gly Gly Gly Gly Gly Gly Ser Gly Gly Ile Gly Tyr Pro Tyr
            740                 745                 750

Pro Arg Ala Pro Val Phe Pro Gly Arg Gly Ser Tyr Ser Asn Arg Gly
        755                 760                 765

Asn Tyr Asn Arg Gly Gly Met Pro Asn Arg Gly Asn Tyr Asn Gln Asn
    770                 775                 780

Phe Arg Gly Arg Gly Asn Asn Arg Gly Tyr Lys Asn Gln Ser Gln Gly
785                 790                 795                 800

Tyr Asn Gln Trp Gln Gln Gly Gln Phe Trp Gly Gln Lys Pro Trp Ser
                805                 810                 815

Gln His Tyr His Gln Gly Tyr Tyr
            820


<210> SEQ ID NO 24
<211> LENGTH: 1178
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Met Leu Lys Phe Arg Thr Val His Gly Gly Leu Arg Leu Leu Gly Ile
  1               5                  10                  15

Arg Arg Thr Ser Thr Ala Pro Ala Ala Ser Pro Asn Val Arg Arg Leu
             20                  25                  30

Glu Tyr Lys Pro Ile Lys Lys Val Met Val Ala Asn Arg Gly Glu Ile
         35                  40                  45

Ala Ile Arg Val Phe Arg Ala Cys Thr Glu Leu Gly Ile Arg Thr Val
     50                  55                  60

Ala Ile Tyr Ser Glu Gln Asp Thr Gly Gln Met His Arg Gln Lys Ala
 65                  70                  75                  80

Asp Glu Ala Tyr Leu Ile Gly Arg Gly Leu Ala Pro Val Gln Ala Tyr
                 85                  90                  95
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Leu His Ile Pro Asp Ile Ile Lys Val Ala Lys Glu Asn Asn Val Asp
            100                 105                 110

Ala Val His Pro Gly Tyr Gly Phe Leu Ser Glu Arg Ala Asp Phe Ala
        115                 120                 125

Gln Ala Cys Gln Asp Ala Gly Val Arg Phe Ile Gly Pro Ser Pro Glu
    130                 135                 140

Val Val Arg Lys Met Gly Asp Lys Val Glu Ala Arg Ala Ile Ala Ile
145                 150                 155                 160

Ala Ala Gly Val Pro Val Val Pro Gly Thr Asp Ala Pro Ile Thr Ser
                165                 170                 175

Leu His Glu Ala His Glu Phe Ser Asn Thr Tyr Gly Phe Pro Ile Ile
            180                 185                 190

Phe Lys Ala Ala Tyr Gly Gly Gly Gly Arg Gly Met Arg Val Val His
        195                 200                 205

Ser Tyr Glu Glu Leu Glu Glu Asn Tyr Thr Arg Ala Tyr Ser Glu Ala
    210                 215                 220

Leu Ala Ala Phe Gly Asn Gly Ala Leu Phe Val Glu Lys Phe Ile Glu
225                 230                 235                 240

Lys Pro Arg His Ile Glu Val Gln Ile Leu Gly Asp Gln Tyr Gly Asn
                245                 250                 255

Ile Leu His Leu Tyr Glu Arg Asp Cys Ser Ile Gln Arg Arg His Gln
            260                 265                 270

Lys Val Val Glu Ile Ala Pro Ala Ala His Leu Asp Pro Gln Leu Arg
        275                 280                 285

Thr Arg Leu Thr Ser Asp Ser Val Lys Leu Ala Lys Gln Val Gly Tyr
    290                 295                 300

Glu Asn Ala Gly Thr Val Glu Phe Leu Val Asp Arg His Gly Lys His
305                 310                 315                 320

Tyr Phe Ile Glu Val Asn Ser Arg Leu Gln Val Glu His Thr Val Thr
                325                 330                 335

Glu Glu Ile Thr Asp Val Asp Leu Val His Ala Gln Ile His Val Ser
            340                 345                 350

Glu Gly Arg Ser Leu Pro Asp Leu Gly Leu Arg Gln Glu Asn Ile Arg
        355                 360                 365

Ile Asn Gly Cys Ala Ile Gln Cys Arg Val Thr Thr Glu Asp Pro Ala
    370                 375                 380

Arg Ser Phe Gln Pro Asp Thr Gly Arg Ile Glu Val Phe Arg Ser Gly
385                 390                 395                 400

Glu Gly Met Gly Ile Arg Leu Asp Asn Ala Ser Ala Phe Gln Gly Ala
                405                 410                 415

Val Ile Ser Pro His Tyr Asp Ser Leu Leu Val Lys Val Ile Ala His
            420                 425                 430

Gly Lys Asp His Pro Thr Ala Ala Thr Lys Met Ser Arg Ala Leu Ala
        435                 440                 445

Glu Phe Arg Val Arg Gly Val Lys Thr Asn Ile Ala Phe Leu Gln Asn
    450                 455                 460

Val Leu Asn Asn Gln Gln Phe Leu Ala Gly Thr Val Asp Thr Gln Phe
465                 470                 475                 480

Ile Asp Glu Asn Pro Glu Leu Phe Gln Leu Arg Pro Ala Gln Asn Arg
                485                 490                 495

Ala Gln Lys Leu Leu His Tyr Leu Gly His Val Met Val Asn Gly Pro
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           500                 505                 510

Thr Thr Pro Ile Pro Val Lys Ala Ser Pro Ser Pro Thr Asp Pro Val
        515                 520                 525

Val Pro Ala Val Pro Ile Gly Pro Pro Pro Ala Gly Phe Arg Asp Ile
    530                 535                 540

Leu Leu Arg Glu Gly Pro Glu Gly Phe Ala Arg Ala Val Arg Asn His
545                 550                 555                 560

Pro Gly Leu Leu Leu Met Asp Thr Thr Phe Arg Asp Ala His Gln Ser
                565                 570                 575

Leu Leu Ala Thr Arg Val Arg Thr His Asp Leu Lys Lys Ile Ala Pro
            580                 585                 590

Tyr Val Ala His Asn Phe Ser Lys Leu Phe Ser Met Glu Asn Trp Gly
        595                 600                 605

Gly Ala Thr Phe Asp Val Ala Met Arg Phe Leu Tyr Glu Cys Pro Trp
    610                 615                 620

Arg Arg Leu Gln Glu Leu Arg Glu Leu Ile Pro Asn Ile Pro Phe Gln
625                 630                 635                 640

Met Leu Leu Arg Gly Ala Asn Ala Val Gly Tyr Thr Asn Tyr Pro Asp
                645                 650                 655

Asn Val Val Phe Lys Phe Cys Glu Val Ala Lys Glu Asn Gly Met Asp
            660                 665                 670

Val Phe Arg Val Phe Asp Ser Leu Asn Tyr Leu Pro Asn Met Leu Leu
        675                 680                 685

Gly Met Glu Ala Ala Gly Ser Ala Gly Gly Val Val Glu Ala Ala Ile
    690                 695                 700

Ser Tyr Thr Gly Asp Val Ala Asp Pro Ser Arg Thr Lys Tyr Ser Leu
705                 710                 715                 720

Gln Tyr Tyr Met Gly Leu Ala Glu Glu Leu Val Arg Ala Gly Thr His
                725                 730                 735

Ile Leu Cys Ile Lys Asp Met Ala Gly Leu Leu Lys Pro Thr Ala Cys
            740                 745                 750

Thr Met Leu Val Ser Ser Leu Arg Asp Arg Phe Pro Asp Leu Pro Leu
        755                 760                 765

His Ile His Thr His Asp Thr Ser Gly Ala Gly Val Ala Ala Met Leu
    770                 775                 780

Ala Cys Ala Gln Ala Gly Ala Asp Val Val Asp Val Ala Ala Asp Ser
785                 790                 795                 800

Met Ser Gly Met Thr Ser Gln Pro Ser Met Gly Ala Leu Val Ala Cys
                805                 810                 815

Thr Arg Gly Thr Pro Leu Asp Thr Glu Val Pro Met Glu Arg Val Phe
            820                 825                 830

Asp Tyr Ser Glu Tyr Trp Glu Gly Ala Arg Gly Leu Tyr Ala Ala Phe
        835                 840                 845

Asp Cys Thr Ala Thr Met Lys Ser Gly Asn Ser Asp Val Tyr Glu Asn
    850                 855                 860

Glu Ile Pro Gly Gly Gln Tyr Thr Asn Leu His Phe Gln Ala His Ser
865                 870                 875                 880

Met Gly Leu Gly Ser Lys Phe Lys Glu Val Lys Lys Ala Tyr Val Glu
                885                 890                 895

Ala Asn Gln Met Leu Gly Asp Leu Ile Lys Val Thr Pro Ser Ser Lys
            900                 905                 910
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Ile Val Gly Asp Leu Ala Gln Phe Met Val Gln Asn Gly Leu Ser Arg
        915                 920                 925

Ala Glu Ala Glu Ala Gln Ala Glu Glu Leu Ser Phe Pro Arg Ser Val
    930                 935                 940

Val Glu Phe Leu Gln Gly Tyr Ile Gly Val Pro His Gly Gly Phe Pro
945                 950                 955                 960

Glu Pro Phe Arg Ser Lys Val Leu Lys Asp Leu Pro Arg Val Glu Gly
                965                 970                 975

Arg Pro Gly Ala Ser Leu Pro Pro Leu Asp Leu Gln Ala Leu Glu Lys
            980                 985                 990

Glu Leu Val Asp Arg His Gly Glu Glu Val Thr Pro Glu Asp Val Leu
        995                1000                1005

Ser Ala Ala Met Tyr Pro Asp Val Phe Ala His Phe Lys Asp Phe Thr
   1010                1015                1020

Ala Thr Phe Gly Pro Leu Asp Ser Leu Asn Thr Arg Leu Phe Leu Gln
1025                1030                1035                1040

Gly Pro Lys Ile Ala Glu Glu Phe Glu Val Glu Leu Glu Arg Gly Lys
               1045                1050                1055

Thr Leu His Ile Lys Ala Leu Ala Val Ser Asp Leu Asn Arg Ala Gly
           1060                1065                1070

Gln Arg Gln Val Phe Phe Glu Leu Asn Gly Gln Leu Arg Ser Ile Leu
       1075                1080                1085

Val Lys Asp Thr Gln Ala Met Lys Glu Met His Phe His Pro Lys Ala
   1090                1095                1100

Leu Lys Asp Val Lys Gly Gln Ile Gly Ala Pro Met Pro Gly Lys Val
1105                1110                1115                1120

Ile Asp Ile Lys Val Val Ala Gly Ala Lys Val Ala Lys Gly Gln Pro
               1125                1130                1135

Leu Cys Val Leu Ser Ala Met Lys Met Glu Thr Val Val Thr Ser Pro
           1140                1145                1150

Met Glu Gly Thr Val Arg Lys Val His Val Thr Lys Asp Met Thr Leu
       1155                1160                1165

Glu Gly Asp Asp Leu Ile Leu Glu Ile Glu
   1170                1175


<210> SEQ ID NO 25
<211> LENGTH: 1178
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Met Leu Lys Phe Arg Thr Val His Gly Gly Leu Arg Leu Leu Gly Ile
  1               5                  10                  15

Arg Arg Thr Ser Thr Ala Pro Ala Ala Ser Pro Asn Val Arg Arg Leu
             20                  25                  30

Glu Tyr Lys Pro Ile Lys Lys Val Met Val Ala Asn Arg Gly Glu Ile
         35                  40                  45

Ala Ile Arg Val Phe Arg Ala Cys Thr Glu Leu Gly Ile Arg Thr Val
     50                  55                  60

Ala Ile Tyr Ser Glu Gln Asp Thr Gly Gln Met His Arg Gln Lys Ala
 65                  70                  75                  80

Asp Glu Ala Tyr Leu Ile Gly Arg Gly Leu Ala Pro Val Gln Ala Tyr
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                85                  90                  95

Leu His Ile Pro Asp Ile Ile Lys Val Ala Lys Glu Asn Asn Val Asp
            100                 105                 110

Ala Val His Pro Gly Tyr Gly Phe Leu Ser Glu Arg Ala Asp Phe Ala
        115                 120                 125

Gln Ala Cys Gln Asp Ala Gly Val Arg Phe Ile Gly Pro Ser Pro Glu
    130                 135                 140

Val Val Arg Lys Met Gly Asp Lys Val Glu Ala Arg Ala Ile Ala Ile
145                 150                 155                 160

Ala Ala Gly Val Pro Val Val Pro Gly Thr Asp Ala Pro Ile Thr Ser
                165                 170                 175

Leu His Glu Ala His Glu Phe Ser Asn Thr Tyr Gly Phe Pro Ile Ile
            180                 185                 190

Phe Lys Ala Ala Tyr Gly Gly Gly Gly Arg Gly Met Arg Val Val His
        195                 200                 205

Ser Tyr Glu Glu Leu Glu Glu Asn Tyr Thr Arg Ala Tyr Ser Glu Ala
    210                 215                 220

Leu Ala Ala Phe Gly Asn Gly Ala Leu Phe Val Glu Lys Phe Ile Glu
225                 230                 235                 240

Lys Pro Arg His Ile Glu Val Gln Ile Leu Gly Asp Gln Tyr Gly Asn
                245                 250                 255

Ile Leu His Leu Tyr Glu Arg Asp Cys Ser Ile Gln Arg Arg His Gln
            260                 265                 270

Lys Val Val Glu Ile Ala Pro Ala Ala His Leu Asp Pro Gln Leu Arg
        275                 280                 285

Thr Arg Leu Thr Ser Asp Ser Val Lys Leu Ala Lys Gln Val Gly Tyr
    290                 295                 300

Glu Asn Ala Gly Thr Val Glu Phe Leu Val Asp Arg His Gly Lys His
305                 310                 315                 320

Tyr Phe Ile Glu Val Asn Ser Arg Leu Gln Val Glu His Thr Val Thr
                325                 330                 335

Glu Glu Ile Thr Asp Val Asp Leu Val His Ala Gln Ile His Val Ser
            340                 345                 350

Glu Gly Arg Ser Leu Pro Asp Leu Gly Leu Arg Gln Glu Asn Ile Arg
        355                 360                 365

Ile Asn Gly Cys Ala Ile Gln Cys Arg Val Thr Thr Glu Asp Pro Ala
    370                 375                 380

Arg Ser Phe Gln Pro Asp Thr Gly Arg Ile Glu Val Phe Arg Ser Gly
385                 390                 395                 400

Glu Gly Met Gly Ile Arg Leu Asp Asn Ala Ser Ala Phe Gln Gly Ala
                405                 410                 415

Val Ile Ser Pro His Tyr Asp Ser Leu Leu Val Lys Val Ile Ala His
            420                 425                 430

Gly Lys Asp His Pro Thr Ala Ala Thr Lys Met Ser Arg Ala Leu Ala
        435                 440                 445

Glu Phe Arg Val Arg Gly Val Lys Thr Asn Ile Ala Phe Leu Gln Asn
    450                 455                 460

Val Leu Asn Asn Gln Gln Phe Leu Ala Gly Thr Val Asp Thr Gln Phe
465                 470                 475                 480

Ile Asp Glu Asn Pro Glu Leu Phe Gln Leu Arg Pro Ala Gln Asn Arg
                485                 490                 495
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Ala Gln Lys Leu Leu His Tyr Leu Gly His Val Met Val Asn Gly Pro
            500                 505                 510

Thr Thr Pro Ile Pro Val Lys Ala Ser Pro Ser Pro Thr Asp Pro Val
        515                 520                 525

Val Pro Ala Val Pro Ile Gly Pro Pro Pro Ala Gly Phe Arg Asp Ile
    530                 535                 540

Leu Leu Arg Glu Gly Pro Glu Gly Phe Ala Arg Ala Val Arg Asn His
545                 550                 555                 560

Pro Gly Leu Leu Leu Met Asp Thr Thr Phe Arg Asp Ala His Gln Ser
                565                 570                 575

Leu Leu Ala Thr Arg Val Arg Thr His Asp Leu Lys Lys Ile Ala Pro
            580                 585                 590

Tyr Val Ala His Asn Phe Ser Lys Leu Phe Ser Met Glu Asn Trp Gly
        595                 600                 605

Gly Ala Thr Phe Asp Val Ala Met Arg Phe Leu Tyr Glu Cys Pro Trp
    610                 615                 620

Arg Arg Leu Gln Glu Leu Arg Glu Leu Ile Pro Asn Ile Pro Phe Gln
625                 630                 635                 640

Met Leu Leu Arg Gly Ala Asn Ala Val Gly Tyr Thr Asn Tyr Pro Asp
                645                 650                 655

Asn Val Val Phe Lys Phe Cys Glu Val Ala Lys Glu Asn Gly Met Asp
            660                 665                 670

Val Phe Arg Val Phe Asp Ser Leu Asn Tyr Leu Pro Asn Met Leu Leu
        675                 680                 685

Gly Met Glu Ala Ala Gly Ser Ala Gly Gly Val Val Glu Ala Ala Ile
    690                 695                 700

Ser Tyr Thr Gly Asp Val Ala Asp Pro Ser Arg Thr Lys Tyr Ser Leu
705                 710                 715                 720

Gln Tyr Tyr Met Gly Leu Ala Glu Glu Leu Val Arg Ala Gly Thr His
                725                 730                 735

Ile Leu Cys Ile Lys Asp Met Ala Gly Leu Leu Lys Pro Thr Ala Cys
            740                 745                 750

Thr Met Leu Val Ser Ser Leu Arg Asp Arg Phe Pro Asp Leu Pro Leu
        755                 760                 765

His Ile His Thr His Asp Thr Ser Gly Ala Gly Val Ala Ala Met Leu
    770                 775                 780

Ala Cys Ala Gln Ala Gly Ala Asp Val Val Asp Val Ala Ala Asp Ser
785                 790                 795                 800

Met Ser Gly Met Thr Ser Gln Pro Ser Met Gly Ala Leu Val Ala Cys
                805                 810                 815

Thr Arg Gly Thr Pro Leu Asp Thr Glu Val Pro Met Glu Arg Val Phe
            820                 825                 830

Asp Tyr Ser Glu Tyr Trp Glu Gly Ala Arg Gly Leu Tyr Ala Ala Phe
        835                 840                 845

Asp Cys Thr Ala Thr Met Lys Ser Gly Asn Ser Asp Val Tyr Glu Asn
    850                 855                 860

Glu Ile Pro Gly Gly Gln Tyr Thr Asn Leu His Phe Gln Ala His Ser
865                 870                 875                 880

Met Gly Leu Gly Ser Lys Phe Lys Glu Val Lys Lys Ala Tyr Val Glu
                885                 890                 895
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Ala Asn Gln Met Leu Gly Asp Leu Ile Lys Val Thr Pro Ser Ser Lys
            900                 905                 910

Ile Val Gly Asp Leu Ala Gln Phe Met Val Gln Asn Gly Leu Ser Arg
        915                 920                 925

Ala Glu Ala Glu Ala Gln Ala Glu Glu Leu Ser Phe Pro Arg Ser Val
    930                 935                 940

Val Glu Phe Leu Gln Gly Tyr Ile Gly Val Pro His Gly Gly Phe Pro
945                 950                 955                 960

Glu Pro Phe Arg Ser Lys Val Leu Lys Asp Leu Pro Arg Val Glu Gly
                965                 970                 975

Arg Pro Gly Ala Ser Leu Pro Pro Leu Asp Leu Gln Ala Leu Glu Lys
            980                 985                 990

Glu Leu Val Asp Arg His Gly Glu Glu Val Thr Pro Glu Asp Val Leu
        995                1000                1005

Ser Ala Ala Met Tyr Pro Asp Val Phe Ala His Phe Lys Asp Phe Thr
   1010                1015                1020

Ala Thr Phe Gly Pro Leu Asp Ser Leu Asn Thr Arg Leu Phe Leu Gln
1025                1030                1035                1040

Gly Pro Lys Ile Ala Glu Glu Phe Glu Val Glu Leu Glu Arg Gly Lys
               1045                1050                1055

Thr Leu His Ile Lys Ala Leu Ala Val Ser Asp Leu Asn Arg Ala Gly
           1060                1065                1070

Gln Arg Gln Val Phe Phe Glu Leu Asn Gly Gln Leu Arg Ser Ile Leu
       1075                1080                1085

Val Lys Asp Thr Gln Ala Met Lys Glu Met His Phe His Pro Lys Ala
   1090                1095                1100

Leu Lys Asp Val Lys Gly Gln Ile Gly Ala Pro Met Pro Gly Lys Val
1105                1110                1115                1120

Ile Asp Ile Lys Val Val Ala Gly Ala Lys Val Ala Lys Gly Gln Pro
               1125                1130                1135

Leu Cys Val Leu Ser Ala Met Lys Met Glu Thr Val Val Thr Ser Pro
           1140                1145                1150

Met Glu Gly Thr Val Arg Lys Val His Val Thr Lys Asp Met Thr Leu
       1155                1160                1165

Glu Gly Asp Asp Leu Ile Leu Glu Ile Glu
   1170                1175


<210> SEQ ID NO 26
<211> LENGTH: 744
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Met Glu Leu Cys Gly Ala Thr Arg Leu Gly Tyr Phe Gly Arg Ser Gln
  1               5                  10                  15

Phe Tyr Ile Ala Leu Lys Leu Val Ala Val Ala Gln Ser Gly Phe Pro
             20                  25                  30

Leu Arg Val Glu Ser Ile Asn Thr Val Lys Asp Leu Pro Leu Pro Arg
         35                  40                  45

Phe Val Ala Ser Lys Asn Glu Gln Glu Ser Arg His Ala Ala Ser Tyr
     50                  55                  60

Ser Ser Asp Ser Glu Asn Gln Gly Ser Tyr Ser Gly Val Ile Pro Pro
 65                  70                  75                  80
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Pro Pro Gly Arg Gly Gln Val Lys Lys Gly Ser Val Ser His Asp Thr
                85                  90                  95

Val Gln Pro Arg Thr Ser Ala Asp Ala Gln Glu Pro Ala Ser Pro Val
            100                 105                 110

Val Ser Pro Gln Gln Ser Pro Pro Thr Ser Pro His Thr Trp Arg Lys
        115                 120                 125

His Ser Arg His Pro Ser Gly Gly Asn Ser Glu Arg Pro Leu Ala Gly
    130                 135                 140

Pro Gly Pro Phe Trp Ser Pro Phe Gly Glu Ala Gln Ser Gly Ser Ser
145                 150                 155                 160

Ala Gly Asp Ala Val Trp Ser Gly His Ser Pro Pro Pro Pro Gln Glu
                165                 170                 175

Asn Trp Val Ser Phe Ala Asp Thr Pro Pro Thr Ser Thr Leu Leu Thr
            180                 185                 190

Met His Pro Ala Ser Val Gln Asp Gln Thr Thr Val Arg Thr Val Ala
        195                 200                 205

Ser Ala Thr Thr Ala Ile Glu Ile Arg Arg Gln Ser Ser Ser Tyr Asp
    210                 215                 220

Asp Pro Trp Lys Ile Thr Asp Glu Gln Arg Gln Tyr Tyr Val Asn Gln
225                 230                 235                 240

Phe Lys Thr Ile Gln Pro Asp Leu Asn Gly Phe Ile Pro Gly Ser Ala
                245                 250                 255

Ala Lys Glu Phe Phe Thr Lys Ser Lys Leu Pro Ile Leu Glu Leu Ser
            260                 265                 270

His Ile Trp Glu Leu Ser Asp Phe Asp Lys Asp Gly Ala Leu Thr Leu
        275                 280                 285

Asp Glu Phe Cys Ala Ala Phe His Leu Val Val Ala Arg Lys Asn Gly
    290                 295                 300

Tyr Asp Leu Pro Glu Lys Leu Pro Glu Ser Leu Met Pro Lys Leu Ile
305                 310                 315                 320

Asp Leu Glu Asp Ser Ala Asp Val Gly Asp Gln Pro Gly Glu Val Gly
                325                 330                 335

Tyr Ser Gly Ser Pro Ala Glu Ala Pro Pro Ser Lys Ser Pro Ser Met
            340                 345                 350

Pro Ser Leu Asn Gln Thr Trp Pro Glu Leu Asn Gln Ser Ser Glu Gln
        355                 360                 365

Trp Glu Thr Phe Ser Glu Arg Ser Ser Ser Ser Gln Thr Leu Thr Gln
    370                 375                 380

Phe Asp Ser Asn Ile Ala Pro Ala Asp Pro Asp Thr Ala Ile Val His
385                 390                 395                 400

Pro Val Pro Ile Arg Met Thr Pro Ser Lys Ile His Met Gln Glu Met
                405                 410                 415

Glu Leu Lys Arg Thr Gly Ser Asp His Thr Asn Pro Thr Ser Pro Leu
            420                 425                 430

Leu Val Lys Pro Ser Asp Leu Leu Glu Glu Asn Lys Ile Asn Ser Ser
        435                 440                 445

Val Lys Phe Ala Ser Gly Asn Thr Val Ala Asp Gly Tyr Ser Ser Ser
    450                 455                 460

Asp Ser Phe Thr Ser Asp Pro Glu Gln Ile Gly Ser Asn Val Thr Arg
465                 470                 475                 480
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Gln Arg Ser His Ser Gly Thr Ser Pro Asp Asn Thr Ala Pro Pro Pro
               485                 490                 495

Pro Pro Pro Arg Pro Gln Pro Ser His Ser Arg Ser Ser Ser Leu Asp
            500                 505                 510

Met Asn Arg Thr Phe Thr Val Thr Thr Gly Gln Gln Gln Ala Gly Val
        515                 520                 525

Val Ala His Pro Pro Ala Val Pro Pro Arg Pro Gln Pro Ser Gln Ala
    530                 535                 540

Pro Gly Pro Ala Val His Arg Pro Val Asp Ala Asp Gly Leu Ile Thr
545                 550                 555                 560

His Thr Ser Thr Ser Pro Gln Gln Ile Pro Glu Gln Pro Asn Phe Val
               565                 570                 575

Asp Phe Ser Gln Phe Glu Val Phe Ala Ala Ser Asn Val Asn Asp Glu
            580                 585                 590

Gln Asp Asp Glu Ala Glu Lys His Pro Glu Val Leu Pro Ala Glu Lys
        595                 600                 605

Ala Ser Asp Pro Ala Ser Ser Leu Arg Val Ala Lys Thr Asp Ser Lys
    610                 615                 620

Thr Glu Glu Lys Thr Ala Ala Ser Ala Pro Ala Asn Val Ser Lys Gly
625                 630                 635                 640

Thr Thr Pro Leu Ala Pro Pro Pro Lys Pro Val Arg Arg Arg Leu Lys
               645                 650                 655

Ser Glu Asp Glu Leu Arg Pro Glu Val Asp Glu His Thr Gln Lys Thr
            660                 665                 670

Gly Val Leu Ala Ala Val Leu Ala Ser Gln Pro Ser Ile Pro Arg Ser
        675                 680                 685

Val Gly Lys Asp Lys Lys Ala Ile Gln Ala Ser Ile Arg Arg Asn Lys
    690                 695                 700

Glu Thr Asn Thr Val Leu Ala Arg Leu Asn Ser Glu Leu Gln Gln Gln
705                 710                 715                 720

Leu Lys Asp Val Leu Glu Glu Arg Ile Ser Leu Glu Val Gln Leu Glu
               725                 730                 735

Gln Leu Arg Pro Phe Ser His Leu
            740
```

<210> SEQ ID NO 27
<211> LENGTH: 1960
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

```
Met Ala Gln Gln Ala Ala Asp Lys Tyr Leu Tyr Val Asp Lys Asn Phe
  1               5                  10                  15

Ile Asn Asn Pro Leu Ala Gln Ala Asp Trp Ala Ala Lys Lys Leu Val
             20                  25                  30

Trp Val Pro Ser Asp Lys Ser Gly Phe Glu Pro Ala Ser Leu Lys Glu
         35                  40                  45

Glu Val Gly Glu Glu Ala Ile Val Glu Leu Val Glu Asn Gly Lys Lys
     50                  55                  60

Val Lys Val Asn Lys Asp Asp Ile Gln Lys Met Asn Pro Pro Lys Phe
 65                  70                  75                  80

Ser Lys Val Glu Asp Met Ala Glu Leu Thr Cys Leu Asn Glu Ala Ser
                 85                  90                  95
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Val Leu His Asn Leu Lys Glu Arg Tyr Tyr Ser Gly Leu Ile Tyr Thr
            100                 105                 110

Tyr Ser Gly Leu Phe Cys Val Val Ile Asn Pro Tyr Lys Asn Leu Pro
        115                 120                 125

Ile Tyr Ser Glu Glu Ile Val Glu Met Tyr Lys Gly Lys Lys Arg His
    130                 135                 140

Glu Met Pro Pro His Ile Tyr Ala Ile Thr Asp Thr Ala Tyr Arg Ser
145                 150                 155                 160

Met Met Gln Asp Arg Glu Asp Gln Ser Ile Leu Cys Thr Gly Glu Ser
                165                 170                 175

Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile Gln Tyr Leu Ala
            180                 185                 190

Tyr Val Ala Ser Ser His Lys Ser Lys Lys Asp Gln Gly Glu Leu Glu
        195                 200                 205

Arg Gln Leu Leu Gln Ala Asn Pro Ile Leu Glu Ala Phe Gly Asn Ala
    210                 215                 220

Lys Thr Val Lys Asn Asp Asn Ser Ser Arg Phe Gly Lys Phe Ile Arg
225                 230                 235                 240

Ile Asn Phe Asp Val Asn Gly Tyr Ile Val Gly Ala Asn Ile Glu Thr
                245                 250                 255

Tyr Leu Leu Glu Lys Ser Arg Ala Ile Arg Gln Ala Lys Glu Glu Arg
            260                 265                 270

Thr Phe His Ile Phe Tyr Tyr Leu Leu Ser Gly Ala Gly Glu His Leu
        275                 280                 285

Lys Thr Asp Leu Leu Leu Glu Pro Tyr Asn Lys Tyr Arg Phe Leu Ser
    290                 295                 300

Asn Gly His Val Thr Ile Pro Gly Gln Gln Asp Lys Asp Met Phe Gln
305                 310                 315                 320

Glu Thr Met Glu Ala Met Arg Ile Met Gly Ile Pro Glu Glu Glu Gln
                325                 330                 335

Met Gly Leu Leu Arg Val Ile Ser Gly Val Leu Gln Leu Gly Asn Ile
            340                 345                 350

Val Phe Lys Lys Glu Arg Asn Thr Asp Gln Ala Ser Met Pro Asp Asn
        355                 360                 365

Thr Ala Ala Gln Lys Val Ser His Leu Leu Gly Ile Asn Val Thr Asp
    370                 375                 380

Phe Thr Arg Gly Ile Leu Thr Pro Arg Ile Lys Val Gly Arg Asp Tyr
385                 390                 395                 400

Val Gln Lys Ala Gln Thr Lys Glu Gln Ala Asp Phe Ala Ile Glu Ala
                405                 410                 415

Leu Ala Lys Ala Thr Tyr Glu Arg Met Phe Arg Trp Leu Val Leu Arg
            420                 425                 430

Ile Asn Lys Ala Leu Asp Lys Thr Lys Arg Gln Gly Ala Ser Phe Ile
        435                 440                 445

Gly Ile Leu Asp Ile Ala Gly Phe Glu Ile Phe Asp Leu Asn Ser Phe
    450                 455                 460

Glu Gln Leu Cys Ile Asn Tyr Thr Asn Glu Lys Leu Gln Gln Leu Phe
465                 470                 475                 480

Asn His Thr Met Phe Ile Leu Glu Gln Glu Glu Tyr Gln Arg Glu Gly
                485                 490                 495
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Ile Glu Trp Asn Phe Ile Asp Phe Gly Leu Asp Leu Gln Pro Cys Ile
            500                 505                 510

Asp Leu Ile Glu Lys Pro Ala Gly Pro Pro Gly Ile Leu Ala Leu Leu
        515                 520                 525

Asp Glu Glu Cys Trp Phe Pro Lys Ala Thr Asp Lys Ser Phe Val Glu
    530                 535                 540

Lys Val Met Gln Glu Gln Gly Thr His Pro Lys Phe Gln Lys Pro Lys
545                 550                 555                 560

Gln Leu Lys Asp Lys Ala Asp Phe Cys Ile Ile His Tyr Ala Gly Lys
                565                 570                 575

Val Asp Tyr Lys Ala Asp Glu Trp Leu Met Lys Asn Met Asp Pro Leu
            580                 585                 590

Asn Asp Asn Ile Ala Thr Leu Leu His Gln Ser Ser Asp Lys Phe Val
        595                 600                 605

Ser Glu Leu Trp Lys Asp Val Asp Arg Ile Ile Gly Leu Asp Gln Val
    610                 615                 620

Ala Gly Met Ser Glu Thr Ala Leu Pro Gly Ala Phe Lys Thr Arg Lys
625                 630                 635                 640

Gly Met Phe Arg Thr Val Gly Gln Leu Tyr Lys Glu Gln Leu Ala Lys
                645                 650                 655

Leu Met Ala Thr Leu Arg Asn Thr Asn Pro Asn Phe Val Arg Cys Ile
            660                 665                 670

Ile Pro Asn His Glu Lys Lys Ala Gly Lys Leu Asp Pro His Leu Val
        675                 680                 685

Leu Asp Gln Leu Arg Cys Asn Gly Val Leu Glu Gly Ile Arg Ile Cys
    690                 695                 700

Arg Gln Gly Phe Pro Asn Arg Val Val Phe Gln Glu Phe Arg Gln Arg
705                 710                 715                 720

Tyr Glu Ile Leu Thr Pro Asn Ser Ile Pro Lys Gly Phe Met Asp Gly
                725                 730                 735

Lys Gln Ala Cys Val Leu Met Ile Lys Ala Leu Glu Leu Asp Ser Asn
            740                 745                 750

Leu Tyr Arg Ile Gly Gln Ser Lys Val Phe Phe Arg Ala Gly Val Leu
        755                 760                 765

Ala His Leu Glu Glu Glu Arg Asp Leu Lys Ile Thr Asp Val Ile Ile
    770                 775                 780

Gly Phe Gln Ala Cys Cys Arg Gly Tyr Leu Ala Arg Lys Ala Phe Ala
785                 790                 795                 800

Lys Arg Gln Gln Gln Leu Thr Ala Met Lys Val Leu Gln Arg Asn Cys
                805                 810                 815

Ala Ala Tyr Leu Lys Leu Arg Asn Trp Gln Trp Trp Arg Leu Phe Thr
            820                 825                 830

Lys Val Lys Pro Leu Leu Gln Val Ser Arg Gln Glu Glu Glu Met Met
        835                 840                 845

Ala Lys Glu Glu Glu Leu Val Lys Val Arg Glu Lys Gln Leu Ala Ala
    850                 855                 860

Glu Asn Arg Leu Thr Glu Met Glu Thr Leu Gln Ser Gln Leu Met Ala
865                 870                 875                 880

Glu Lys Leu Gln Leu Gln Glu Gln Leu Gln Ala Glu Thr Glu Leu Cys
                885                 890                 895

Ala Glu Ala Glu Glu Leu Arg Ala Arg Leu Thr Ala Lys Lys Gln Glu
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           900                 905                 910

Leu Glu Glu Ile Cys His Asp Leu Glu Ala Arg Val Glu Glu Glu Glu
        915                 920                 925

Glu Arg Cys Gln His Leu Gln Ala Glu Lys Lys Lys Met Gln Gln Asn
    930                 935                 940

Ile Gln Glu Leu Glu Glu Gln Leu Glu Glu Glu Glu Ser Ala Arg Gln
945                 950                 955                 960

Lys Leu Gln Leu Glu Lys Val Thr Thr Glu Ala Lys Leu Lys Lys Leu
                965                 970                 975

Glu Glu Glu Gln Ile Ile Leu Glu Asp Gln Asn Cys Lys Leu Ala Lys
            980                 985                 990

Glu Lys Lys Leu Leu Glu Asp Arg Ile Ala Glu Phe Thr Thr Asn Leu
        995                1000                1005

Thr Glu Glu Glu Glu Lys Ser Lys Ser Leu Ala Lys Leu Lys Asn Lys
   1010                1015                1020

His Glu Ala Met Ile Thr Asp Leu Glu Glu Arg Leu Arg Arg Glu Glu
1025                1030                1035                1040

Lys Gln Arg Gln Glu Leu Glu Lys Thr Arg Arg Lys Leu Glu Gly Asp
               1045                1050                1055

Ser Thr Asp Leu Ser Asp Gln Ile Ala Glu Leu Gln Ala Gln Ile Ala
           1060                1065                1070

Glu Leu Lys Met Gln Leu Ala Lys Lys Glu Glu Glu Leu Gln Ala Ala
       1075                1080                1085

Leu Ala Arg Val Glu Glu Glu Ala Ala Gln Lys Asn Met Ala Leu Lys
   1090                1095                1100

Lys Ile Arg Glu Leu Glu Ser Gln Ile Ser Glu Leu Gln Glu Asp Leu
1105                1110                1115                1120

Glu Ser Glu Arg Ala Ser Arg Asn Lys Ala Glu Lys Gln Lys Arg Asp
               1125                1130                1135

Leu Gly Glu Glu Leu Glu Ala Leu Lys Thr Glu Leu Glu Asp Thr Leu
           1140                1145                1150

Asp Ser Thr Ala Ala Gln Gln Glu Leu Arg Ser Lys Arg Glu Gln Glu
       1155                1160                1165

Val Asn Ile Leu Lys Lys Thr Leu Glu Glu Glu Ala Lys Thr His Glu
   1170                1175                1180

Ala Gln Ile Gln Glu Met Arg Gln Lys His Ser Gln Ala Val Glu Glu
1185                1190                1195                1200

Leu Ala Glu Gln Leu Glu Gln Thr Lys Arg Val Lys Ala Asn Leu Glu
               1205                1210                1215

Lys Ala Lys Gln Thr Leu Glu Asn Glu Arg Gly Glu Leu Ala Asn Glu
           1220                1225                1230

Val Lys Val Leu Leu Gln Gly Lys Gly Asp Ser Glu His Lys Arg Lys
       1235                1240                1245

Lys Val Glu Ala Gln Leu Gln Glu Leu Gln Val Lys Phe Asn Glu Gly
   1250                1255                1260

Glu Arg Val Arg Thr Glu Leu Ala Asp Lys Val Thr Lys Leu Gln Val
1265                1270                1275                1280

Glu Leu Asp Asn Val Thr Gly Leu Leu Ser Gln Ser Asp Ser Lys Ser
               1285                1290                1295

Ser Lys Leu Thr Lys Asp Phe Ser Ala Leu Glu Ser Gln Leu Gln Asp
           1300                1305                1310
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Thr Gln Glu Leu Leu Gln Glu Glu Asn Arg Gln Lys Leu Ser Leu Ser
       1315                1320                1325

Thr Lys Leu Lys Gln Val Glu Asp Glu Lys Asn Ser Phe Arg Glu Gln
   1330                1335                1340

Leu Glu Glu Glu Glu Glu Ala Lys His Asn Leu Glu Lys Gln Ile Ala
1345                1350                1355                1360

Thr Leu His Ala Gln Val Ala Asp Met Lys Lys Lys Met Glu Asp Ser
               1365                1370                1375

Val Gly Cys Leu Glu Thr Ala Glu Glu Val Lys Arg Lys Leu Gln Lys
           1380                1385                1390

Asp Leu Glu Gly Leu Ser Gln Arg His Glu Glu Lys Val Ala Ala Tyr
       1395                1400                1405

Asp Lys Leu Glu Lys Thr Lys Thr Arg Leu Gln Gln Glu Leu Asp Asp
   1410                1415                1420

Leu Leu Val Asp Leu Asp His Gln Arg Gln Ser Ala Cys Asn Leu Glu
1425                1430                1435                1440

Lys Lys Gln Lys Lys Phe Asp Gln Leu Leu Ala Glu Glu Lys Thr Ile
               1445                1450                1455

Ser Ala Lys Tyr Ala Glu Glu Arg Asp Arg Ala Glu Ala Glu Ala Arg
           1460                1465                1470

Glu Lys Glu Thr Lys Ala Leu Ser Leu Ala Arg Ala Leu Glu Glu Ala
       1475                1480                1485

Met Glu Gln Lys Ala Glu Leu Glu Arg Leu Asn Lys Gln Phe Arg Thr
   1490                1495                1500

Glu Met Glu Asp Leu Met Ser Ser Lys Asp Asp Val Gly Lys Ser Val
1505                1510                1515                1520

His Glu Leu Glu Lys Ser Lys Arg Ala Leu Glu Gln Gln Val Glu Glu
               1525                1530                1535

Met Lys Thr Gln Leu Glu Glu Leu Glu Asp Glu Leu Gln Ala Thr Glu
           1540                1545                1550

Asp Ala Lys Leu Arg Leu Glu Val Asn Leu Gln Ala Met Lys Ala Gln
       1555                1560                1565

Phe Glu Arg Asp Leu Gln Gly Arg Asp Glu Gln Ser Glu Glu Lys Lys
   1570                1575                1580

Lys Gln Leu Val Arg Gln Val Arg Glu Met Glu Ala Glu Leu Glu Asp
1585                1590                1595                1600

Glu Arg Lys Gln Arg Ser Met Ala Val Ala Ala Arg Lys Lys Leu Glu
               1605                1610                1615

Met Asp Leu Lys Asp Leu Glu Ala His Ile Asp Ser Ala Asn Lys Asn
           1620                1625                1630

Arg Asp Glu Ala Ile Lys Gln Leu Arg Lys Leu Gln Ala Gln Met Lys
       1635                1640                1645

Asp Cys Met Arg Glu Leu Asp Asp Thr Arg Ala Ser Arg Glu Glu Ile
   1650                1655                1660

Leu Ala Gln Ala Lys Glu Asn Glu Lys Lys Leu Lys Ser Met Glu Ala
1665                1670                1675                1680

Glu Met Ile Gln Leu Gln Glu Glu Leu Ala Ala Ala Glu Arg Ala Lys
               1685                1690                1695

Arg Gln Ala Gln Gln Glu Arg Asp Glu Leu Ala Asp Glu Ile Ala Asn
           1700                1705                1710
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Ser Ser Gly Lys Gly Ala Leu Ala Leu Glu Glu Lys Arg Arg Leu Glu
       1715                1720                1725

Ala Arg Ile Ala Gln Leu Glu Glu Glu Leu Glu Glu Glu Gln Gly Asn
   1730                1735                1740

Thr Glu Leu Ile Asn Asp Arg Leu Lys Lys Ala Asn Leu Gln Ile Asp
1745                1750                1755                1760

Gln Ile Asn Thr Asp Leu Asn Leu Glu Arg Ser His Ala Gln Lys Asn
               1765                1770                1775

Glu Asn Ala Arg Gln Gln Leu Glu Arg Gln Asn Lys Glu Leu Lys Val
           1780                1785                1790

Lys Leu Gln Glu Met Glu Gly Thr Val Lys Ser Lys Tyr Lys Ala Ser
       1795                1800                1805

Ile Thr Ala Leu Glu Ala Lys Ile Ala Gln Leu Glu Glu Gln Leu Asp
   1810                1815                1820

Asn Glu Thr Lys Glu Arg Gln Ala Ala Cys Lys Gln Val Arg Arg Thr
1825                1830                1835                1840

Glu Lys Lys Leu Lys Asp Val Leu Leu Gln Val Asp Asp Glu Arg Arg
               1845                1850                1855

Asn Ala Glu Gln Tyr Lys Asp Gln Ala Asp Lys Ala Ser Thr Arg Leu
           1860                1865                1870

Lys Gln Leu Lys Arg Gln Leu Glu Glu Ala Glu Glu Glu Ala Gln Arg
       1875                1880                1885

Ala Asn Ala Ser Arg Arg Lys Leu Gln Arg Glu Leu Glu Asp Ala Thr
   1890                1895                1900

Glu Thr Ala Asp Ala Met Asn Arg Glu Val Ser Ser Leu Lys Asn Lys
1905                1910                1915                1920

Leu Arg Arg Gly Asp Leu Pro Phe Val Val Pro Arg Arg Met Ala Arg
               1925                1930                1935

Lys Gly Ala Gly Asp Gly Ser Asp Glu Glu Val Asp Gly Lys Ala Asp
           1940                1945                1950

Gly Ala Glu Ala Lys Pro Ala Glu
       1955                1960


<210> SEQ ID NO 28
<211> LENGTH: 679
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Ile Ser Ala Ser Arg Ala Ala Ala Ala Arg Leu Val Gly Ala Ala
  1               5                  10                  15

Ala Ser Arg Gly Pro Thr Ala Ala Arg His Gln Asp Ser Trp Asn Gly
             20                  25                  30

Leu Ser His Glu Ala Phe Arg Leu Val Ser Arg Arg Asp Tyr Ala Ser
         35                  40                  45

Glu Ala Ile Lys Gly Ala Val Val Gly Ile Asp Leu Gly Thr Thr Asn
     50                  55                  60

Ser Cys Val Ala Val Met Glu Gly Lys Gln Ala Lys Val Leu Glu Asn
 65                  70                  75                  80

Ala Glu Gly Ala Arg Thr Thr Pro Ser Val Val Ala Phe Thr Ala Asp
                 85                  90                  95

Gly Glu Arg Leu Val Gly Met Pro Ala Lys Arg Gln Ala Val Thr Asn
            100                 105                 110
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Pro Asn Asn Thr Phe Tyr Ala Thr Lys Arg Leu Ile Gly Arg Arg Tyr
        115                 120                 125

Asp Asp Pro Glu Val Gln Lys Asp Ile Lys Asn Val Pro Phe Lys Ile
    130                 135                 140

Val Arg Ala Ser Asn Gly Asp Ala Trp Val Glu Ala His Gly Lys Leu
145                 150                 155                 160

Tyr Ser Pro Ser Gln Ile Gly Ala Phe Val Leu Met Lys Met Lys Glu
                165                 170                 175

Thr Ala Glu Asn Tyr Leu Gly His Thr Ala Lys Asn Ala Val Ile Thr
            180                 185                 190

Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp Ala
        195                 200                 205

Gly Gln Ile Ser Gly Leu Asn Val Leu Arg Val Ile Asn Glu Pro Thr
    210                 215                 220

Ala Ala Ala Leu Ala Tyr Gly Leu Asp Lys Ser Glu Asp Lys Val Ile
225                 230                 235                 240

Ala Val Tyr Asp Leu Gly Gly Gly Thr Phe Asp Ile Ser Ile Leu Glu
                245                 250                 255

Ile Gln Lys Gly Val Phe Glu Val Lys Ser Thr Asn Gly Asp Thr Phe
            260                 265                 270

Leu Gly Gly Glu Asp Phe Asp Gln Ala Leu Leu Arg His Ile Val Lys
        275                 280                 285

Glu Phe Lys Arg Glu Thr Gly Val Asp Leu Thr Lys Asp Asn Met Ala
    290                 295                 300

Leu Gln Arg Val Arg Glu Ala Ala Glu Lys Ala Lys Cys Glu Leu Ser
305                 310                 315                 320

Ser Ser Val Gln Thr Asp Ile Asn Leu Pro Tyr Leu Thr Met Asp Ser
                325                 330                 335

Ser Gly Pro Lys His Leu Asn Met Lys Leu Thr Arg Ala Gln Phe Glu
            340                 345                 350

Gly Ile Val Thr Asp Leu Ile Arg Arg Thr Ile Ala Pro Cys Gln Lys
        355                 360                 365

Ala Met Gln Asp Ala Glu Val Ser Lys Ser Asp Ile Gly Glu Val Ile
    370                 375                 380

Leu Val Gly Gly Met Thr Arg Met Pro Lys Val Gln Gln Thr Val Gln
385                 390                 395                 400

Asp Leu Phe Gly Arg Ala Pro Ser Lys Ala Val Asn Pro Asp Glu Ala
                405                 410                 415

Val Ala Ile Gly Ala Ala Ile Gln Gly Gly Val Leu Ala Gly Asp Val
            420                 425                 430

Thr Asp Val Leu Leu Leu Asp Val Thr Pro Leu Ser Leu Gly Ile Glu
        435                 440                 445

Thr Leu Gly Gly Val Phe Thr Lys Leu Ile Asn Arg Asn Thr Thr Ile
    450                 455                 460

Pro Thr Lys Lys Ser Gln Val Phe Ser Thr Ala Ala Asp Gly Gln Thr
465                 470                 475                 480

Gln Val Glu Ile Lys Val Cys Gln Gly Glu Arg Glu Met Ala Gly Asp
                485                 490                 495

Asn Lys Leu Leu Gly Gln Phe Thr Leu Ile Gly Ile Pro Pro Ala Pro
            500                 505                 510
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Arg Gly Val Pro Gln Ile Glu Val Thr Phe Asp Ile Asp Ala Asn Gly
        515                 520                 525

Ile Val His Val Ser Ala Lys Asp Lys Gly Thr Gly Arg Glu Gln Gln
    530                 535                 540

Ile Val Ile Gln Ser Ser Gly Gly Leu Ser Lys Asp Asp Ile Glu Asn
545                 550                 555                 560

Met Val Lys Asn Ala Glu Lys Tyr Ala Glu Glu Asp Arg Arg Lys Lys
                565                 570                 575

Glu Arg Val Glu Ala Val Asn Met Ala Glu Gly Ile Ile His Asp Thr
            580                 585                 590

Glu Thr Lys Met Glu Glu Phe Lys Asp Gln Leu Pro Ala Asp Glu Cys
        595                 600                 605

Asn Lys Leu Lys Glu Glu Ile Ser Lys Met Arg Glu Leu Leu Ala Arg
    610                 615                 620

Lys Asp Ser Glu Thr Gly Glu Asn Ile Arg Gln Ala Ala Ser Ser Leu
625                 630                 635                 640

Gln Gln Ala Ser Leu Lys Leu Phe Glu Met Ala Tyr Lys Lys Met Ala
                645                 650                 655

Ser Glu Arg Glu Gly Ser Gly Ser Ser Gly Thr Gly Glu Gln Lys Glu
            660                 665                 670

Asp Gln Lys Glu Glu Lys Gln
        675


<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Val Thr Glu Pro Gly Thr Ala Gln Tyr
  1               5


<210> SEQ ID NO 30
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic siRNA oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      siRNA oligonucleotide

<400> SEQUENCE: 30

cuggaaguca agcuccucct t                                              21


<210> SEQ ID NO 31
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic siRNA oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      siRNA oligonucleotide

<400> SEQUENCE: 31

ccagucgcaa acgcgacugt t                                              21
```

1. A method for identifying an insulin response modulator, comprising contacting a composition comprising Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate an activity selected from the group consisting of:

(a) an interaction of Akt or the Akt bioactive fragment to the substrate or the substrate bioactive fragment;

(b) an activity of Akt or the Akt bioactive fragment;

(c) an activity of the substrate or the substrate bioactive fragment; and

(d) the phosphorylation state of the Akt substrate or the substrate bioactive fragment;

such that the insulin response modulator is identified.

2-4. (canceled)

5. The method of claim 1, wherein the interaction of Akt or the Akt bioactive fragment to the substrate or the substrate bioactive fragment comprises binding of Akt or the Akt bioactive fragment to the substrate or the substrate bioactive fragment.

6. The method of claim 1, wherein the Akt substrate is selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75).

7. The method of any one of claim 1, wherein the Akt comprises Akt1 or Akt2.

8. The method of claim 1, wherein at least one of Akt, the Akt bioactive fragment, the Akt substrate or the substrate bioactive fragment is detectably labeled.

9. The method of claim 1, wherein at least one of Akt, the Akt bioactive fragment, the Akt substrate or the substrate bioactive fragment is radioactively labeled.

10. The method of claim 1, wherein at least one of Akt, the Akt bioactive fragment, the Akt substrate or the substrate bioactive fragment is fluorescently labeled.

11. The method of claim 1, wherein the interaction is compared to an appropriate control.

12. The method of claim 1, wherein the activity is compared to an appropriate control.

13. The method of claim 1, wherein the phosphorylation state is compared to an appropriate control.

14. The method of claim 1, wherein at least one of Akt, the Akt bioactive fragment, the Akt substrate or the substrate bioactive fragment is immobilized.

15. The method of claim 1, wherein the activity of Akt or the bioactive fragment thereof is selected from the group consisting of regulation of insulin signaling to glycogen synthase kinase, regulation of intracellular GLUT4 trafficking and regulation of intracellular retention of GLUT4.

16. The method of claim 1, wherein the activity of the Akt substrate or substrate bioactive fragment is an activity set forth in Table 1 or in subsections IA-IQ.

17. The method of claim 1, wherein the Akt substrate is R-type calcium channel alpha 1E subunit.

18. The method of claim 1, wherein the Akt substrate is WNK1.

19. The method of claim 1, wherein the Akt substrate is ribosomal protein L6, and the activity comprises involvement in phosphorylation.

20. The method of claim 1, wherein the Akt substrate is guanine nucleotide exchange factor Lbc (GEF Lbc).

21. The method of claim 1, wherein the Akt substrate is ATP citrate lyase.

22. The method of claim 1, wherein the Akt bioactive fragment comprises an Akt substrate interacting portion of Akt.

23. A method for identifying an insulin response modulator, comprising contacting a cell that expresses an Akt substrate or a bioactive fragment thereof and Akt or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate an activity selected from the group consisting of:

(a) an interaction of the Akt substrate or the substrate bioactive fragment to Akt or the Akt bioactive fragment;

(b) an activity of the Akt or the Akt bioactive fragment;

(c) an activity of the Akt substrate or the substrate bioactive fragment: and

(d) the phosphorylation state of the Akt substrate or the substrate bioactive fragment;

such that the insulin response modulator is identified.

24-26. (canceled)

27. The method of claim 23, wherein the interaction of Akt or the Akt bioactive fragment to the substrate or the substrate bioactive fragment comprises binding of Akt or the Akt bioactive fragment to the substrate or the substrate bioactive fragment.

28. The method of claim 23, wherein the Akt substrate is selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75).

29. The method of claim 23, wherein the activity of Akt or the bioactive fragment thereof is selected from the group consisting of regulation of insulin signaling to glycogen synthase kinase, regulation of intracellular GLUT4 trafficking and regulation of intracellular retention of GLUT4.

30. The method of claim 23, wherein the activity of the substrate is an activity set forth in Table 1 or in subsections IA-IQ.

31. The method of claim 23, wherein the Akt comprises Akt1 or Akt2.

32. The method of claim 23, wherein the Akt substrate is R-type calcium channel alpha 1E subunit.

33. The method of claim 23, wherein the Akt substrate is WNK1.

34. The method of claim 23, wherein the Akt substrate is ribosomal protein L6, and the activity comprises involvement in phosphorylation.

35. The method of claim 23, wherein the Akt substrate is guanine nucleotide exchange factor Lbc (GEF Lbc).

36. The method of claim 23, wherein the Akt substrate is ATP citrate lyase.

37. The method of claim 23, wherein the Akt bioactive fragment comprises an Akt substrate interacting portion of Akt.

38. The method of claim 23, wherein said cell overexpresses the Akt substrate or the bioactive fragment thereof.

39. The method of claim 23, wherein said cell overexpresses Akt or the bioactive fragment thereof.

40. The method of claim 23, wherein said cell overexpresses the Akt substrate or the substrate bioactive fragment and Akt or the Akt bioactive fragment.

41. The method of claim 1 or 23, wherein the modulator identified is a positive modulator.

42. The method of claim 1 or 23, wherein the modulator identified is a negative modulator.

43. A modulator identified by claim 1 or 23.

44. A method for identifying an Akt:Akt substrate modulator, comprising contacting a cell or a composition comprising Akt or a bioactive fragment thereof and an Akt substrate or a bioactive fragment thereof with a test compound and determining the ability of the test compound to affect an activity selected from the group consisting of:

(a) an interaction of the Akt or the bioactive fragment thereof to the Akt substrate or the bioactive fragment thereof;

(b) an activity of the Akt or the bioactive fragment thereof;

(c) an activity of the substrate or the bioactive fragment thereof; and

(d) the phosphorylation state of the Akt substrate or the bioactive fragment thereof;

such that the modulator is identified.

45-47. (canceled)

48. The method of claim 44 wherein the interaction of the Akt or the bioactive fragment thereof to the substrate or the bioactive fragment thereof is the binding of the Akt or the bioactive fragment thereof to the substrate or the bioactive fragment thereof.

49. The method of claim 44, wherein the ability of the test compound to affect comprises the ability of the test compound to either enhance or inhibit.

50. The method claim 44, wherein the Akt substrate is selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75).

51. The method of any one of claim 44, wherein the Akt comprises Akt1 or Akt2.

52. A method of modulating insulin responsiveness in a subject comprising administering to the subject an insulin response modulator identified according to the methods of any one of claims **1**, **23** or **44** such that insulin responsiveness is modulated.

53. A method of regulating glucose transport in a subject comprising administering to the subject an insulin response modulator identified according to the methods of any one of claims **1**, **23** or **44** such that glucose transport is regulated.

54. A method of regulating gluconeogenesis in a subject comprising administering to the subject an insulin response modulator identified according to the methods of any one of claims **1**, **23** or **44** such that gluconeogenesis is regulated.

55. A method of regulating glucose homeostasis in a subject comprising administering to the subject an insulin response modulator identified according to the methods of any one of claims **1**, **23** or **44** such that glucose homeostasis is regulated.

56. A method of regulating blood glucose levels in a subject comprising administering to the subject an insulin response modulator identified according to the methods of any one of claims **1**, **23** or **44**, such that blood glucose levels are regulated.

57. An antibody that specifically binds to an Akt-interacting domain of an Akt substrate, said antibody being capable of interfering with the Akt:Akt substrate interaction.

58. The method of claim 57, wherein the Akt substrate is selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75).

59. A pharmaceutical composition comprising the antibody of claim 57.

60. A pharmaceutical composition comprising the modulator of claim 43.

61. A pharmaceutical composition comprising an Akt-interacting domain of an Akt substrate, said Akt-interacting domain being capable of interfering with the Akt:Akt substrate interaction.

62. The composition of claim 61, wherein the Akt substrate is selected from the group consisting of R-type calcium channel alpha-1E subunit (R-CaC1E), WNK1, FMS interacting protein (FMIP), nGAP-like protein, nuclear

matrix protein p84, HIRA interacting protein 3 (HIRIP3), HSP71, ribosomal protein L6, guanine nucleotide exchange factor Lbc (GEF Lbc), ATP citrate lyase, Mi-2b, peripheral benzodiazepine receptor-associated protein 1, heterogeneous nuclear ribonucleoprotein U (hnRNP U protein), pyruvate carboxylase precursor, Eps domain containing protein (RalBP1), nonmuscle myosin IIA (NMMIIA), and stress 70 protein (p66 mot1/GRP75).

63. A method of treating an insulin response disease or disorder comprising administering the pharmaceutical composition of claim 59 or 61.

64. The method of claim 63, wherein the disease or disorder is selected from the group consisting of Type I diabetes, Type II diabetes, and insulin resistance.

65. A method of treating an insulin response disease or disorder comprising administering the pharmaceutical composition of claim 60.

66. The method of claim 65, wherein the disease or disorder is selected from the group consisting of Type I diabetes, Type II diabetes, and insulin resistance.

* * * * *

专利名称(译)	鉴定胰岛素反应调节剂的方法及其用途		
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摘要(译)

提供了鉴定胰岛素响应调节剂的方法。特别是，识别Akt调节剂及其相关底物（包括R型钙通道α-1E亚基（R-CaC1E），WNK1，FMS相互作用蛋白（FMIP），nGAP样蛋白，核基质蛋白p84， HIRA相互作用蛋白3（HIRIP3），HSP71，核糖体蛋白L6，鸟嘌呤核苷酸交换因子Lbc（GEF Lbc），ATP柠檬酸裂解酶，Mi-2b，外周苯并二氮杂受体相关蛋白1，异质核核糖核蛋白U（hnRNP U蛋白），提供丙酮酸羧化酶前体，含有Eps结构域的蛋白质（RalBP1），非肌肉肌球蛋白IIA（NMMIIA）和应激70蛋白质（p66 mot1 / GRP75），或与其相关的活性。利用根据本发明方法鉴定的化合物的治疗方法还提供。

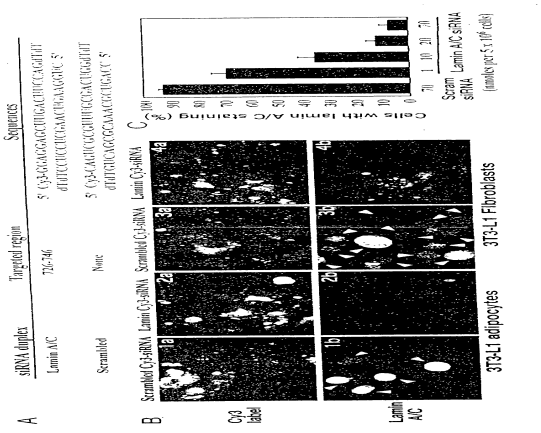

FIGURE 1